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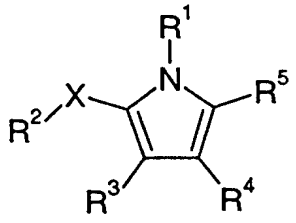
(54) Title: PYRROLE DERIVATIVES FOR TREATING AIDS



(I)

(57) Abstract: The invention is concerned with novel pyrrole derivatives, a prcess for their manufacture, pharmaceutical compositions and the use of such compounds in medecine. In particular, the compounds of formula (I) are inhibitors of the human immunodeficiency virus reverse transcriptase enzyme which is involved in viral replication. Consequently the compounds of this invention may be advantageously used as therapeutic agents for HIV mediated process. The invention describes novel compounds of formula (I) wherein R^1 is alkyl, cycloalkyl, aryl or heterocyclyl; R^2 is alkyl, cycloalkyl, aryl or heterocyclyl; R^3 is hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl; R^4 is hydrogen, alkyl, carboxyl, C(=O)R, CONR'R'', cyano or alkenyl, wherein R is hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl, and wherein R' and R'', are independantly of each other, hydrogen, alkyl or aryl; R^5 is alkyl, aryl or a group -Z-C(=O)R''', wherein Z is a single bond or -CH=CH-, and wherein R''' is hydrogen or alkyl; X represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together CH_2-aryl or CH_2-heterocyclyl; and with the proviso that only one of R^3 and R^4 is hydrogen and alkyl in R^3 is not CF_3; and hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof.

PYRROLE DERIVATIVES FOR TREATING AIDS

The invention is concerned with novel pyrrole derivatives, a process for their manufacture, pharmaceutical compositions and the use of such compounds in medicine, especially in the treatment of viral diseases. In particular, the compounds are inhibitors of the human immunodeficiency virus reverse transcriptase enzyme which is involved in viral replication. Consequently the compounds of this invention may be advantageously used as therapeutic agents for the treatment of diseases mediated by the human immunodeficiency virus (HIV).

The disease Acquired Immunodeficiency Syndrome (AIDS) is the end result of infection by the distinct retroviruses, human immunodeficiency virus type-1 (HIV-1) or type-2 (HIV-2). Several critical points in the virus's life cycle have been identified as possible targets for therapeutic intervention. Inhibition of one of these, the transcription of viral RNA to viral DNA (reverse transcriptase, RT), has provided a number of the current therapies used in treating AIDS. Inhibition of reverse transcriptase provided the first form of treatment for HIV infection with 3'-azido-3'-deoxythymidine (AZT). Since then several inhibitors have been launched, broadly forming two classes: nucleoside analogues and non-nucleosides. As an example of the latter it has been found that certain benzoxazinones, e.g. efavirenz are useful in the inhibition of HIV RT. However, development of strains of the virus resistant to current RT inhibitors is a constant problem. Therefore, development of compounds effective against resistant strains is an important goal.

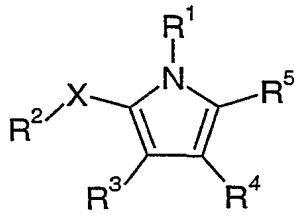
Meanwhile, explorations into pyrrole derivatives have been undertaken with the view of utilising them as medicines.

US Patent 3,644,631 describes pyrrole derivatives effective for the therapy of inflammatory syndromes.

US Patent 4,282,242 describes pyrrole derivatives effective for the therapy of lowering the blood glucose level in hyperglycemic mammals.

The object of the present invention is to provide novel compounds which are potent inhibitors of the human immunodeficiency virus reverse transcriptase enzyme, which is involved in viral replication, and which accordingly show a potential to be efficacious as antiviral drugs.

This object could be achieved with the compounds of formula I



I

wherein

R^1 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^2 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^3 is hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R, CONR'R", cyano or alkenyl, wherein

R is hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl, and wherein

R' and R", are independently of each other, hydrogen, alkyl or aryl;

R^5 is alkyl, aryl or a group -Z-C(=O)R"', wherein

Z is a single bond or –CH=CH-, and wherein

R"' is hydrogen or alkyl;

X represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that

only one of R^3 and R^4 is hydrogen and alkyl in R^3 is not CF_3; and

hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof.

The term "alkyl" as used herein, and if not specified by the number of carbon atoms, denotes an optionally substituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, pentyl, hexyl, heptyl, including their different isomers.

Suitable substituents for the alkyl chain can be selected from one or more of

aryl, heterocyclyl,

carboxyl,

alkoxy, cycloalkyl oxy, aryl oxy, heterocyclyl oxy, hydroxy,

amino carbonyl oxy, alkyl amino carbonyl oxy, dialkyl amino carbonyl oxy, aryl amino carbonyl oxy, heterocyclyl amino carbonyl oxy,

alkyl carbonyl, cycloalkyl carbonyl, aryl carbonyl, heterocyclyl carbonyl,

hydroxy carbonyl, alkoxy carbonyl, cycloalkyl oxy carbonyl, aryl oxy carbonyl, heterocyclyl oxy carbonyl,

amino carbonyl, alkyl amino carbonyl, dialkyl amino carbonyl, cycloalkyl amino carbonyl, aryl amino carbonyl, heterocyclyl amino carbonyl,

amino, alkyl amino, dialkyl amino, cycloalkyl amino, aryl amino, heterocyclyl amino,

alkyl carbonyl amino, cycloalkyl carbonyl amino, aryl carbonyl amino, heterocyclyl carbonyl amino,

alkoxy carbonyl amino, cycloalkyl oxy carbonyl amino, aryloxy carbonyl amino, heterocylyl oxy carbonyl amino,
alkyl amino carbonyl amino, dialkyl amino carbonyl amino, cycloalkyl amino carbonyl amino, aryl amino carbonyl amino, heterocyclyl amino carbonyl amino,
alkyl sulfonyl amino, cycloalkyl sulfonyl amino, aryl sulfonyl amino, heterocyclyl sulfonyl amino,
nitro,

alkyl sulfinyl, cycloalkyl sulfinyl, aryl sulfinyl, heterocyclyl sulfinyl,

alkyl sulfonyl, cycloalkyl sulfonyl, aryl sulfonyl, heterocyclyl sulfonyl,

alkyl thio, cycloalkyl thio, aryl thio, heterocyclyl thio or

halogen.

In case more than one substituent is attached to the alkyl group, these substituents can be identical or different from each other.

The suitable substituents for the alkyl group aryl and heterocyclyl may be substituted with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from C_{1-4}-alkyl (preferably methyl), C_{1-4}-alkoxy (preferably methoxy), halogen (preferably chlorine) or trifluoromethyl. Examples for substituted alkyl are cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 2-pyridylbutyl, methyl-2-pyridyl-methyl, methyl-2-pyridyl-ethyl, dimethyl-2-pyridyl-methyl, ethyl-2-pyridyl-methyl, methoxy-2-pyridyl-methyl, methoxy-2-pyridyl-ethyl, dimethoxy-2-pyridyl-methyl, fluoro-2-pyridyl-methyl, difluoro-2-pyridyl-methyl, chloro-2-pyridyl-methyl, chloro-2-pyridyl-ethyl, dichloro-2-pyridyl-methyl, dichloro-2-pyridyl-methyl, bromo-2-pyridyl-methyl, dibromo-2-pyridyl-methyl, 3-pyridyl-methyl, 3-pyridyl-ethyl, 3-pyridyl-propyl, 3-pyridyl-butyl, methyl-3-pyridyl-methyl, methyl-3-pyridyl-ethyl, dimethyl-3-pyridyl-methyl, ethyl-3-pyridyl-methyl, methoxy-3-pyridyl-methyl, methoxy-3-pyridyl-ethyl, dimethoxy-3-pyridyl-methyl, fluoro-3-pyridyl-methyl, difluoro-3-pyridyl-methyl, chloro-3-pyridyl-methyl, chloro-3-pyridyl-ethyl, dichloro-3-pyridyl-methyl, dichloro-3-pyridyl-methyl, bromo-3-pyridyl-methyl, dibromo-3-pyridyl-methyl, 4-pyridyl-methyl, 4-pyridyl-ethyl, 4-pyridyl-propyl, 4-pyridyl-butyl, methyl-4-pyridyl-methyl, methyl-4-pyridyl-ethyl, dimethyl-4-pyridyl-methyl, ethyl-4-pyridyl-methyl, 2-(trifluoromethyl)-4-pyridyl-1-methyl, 3-(trifluoromethyl)-4-pyridyl-1-methyl, 2-(trifluoromethyl)-3-pyridyl-1-methyl, 4-(trifluoromethyl)-3-pyridyl-1-methyl, 3-(trifluoromethyl)-2-pyridyl-1-methyl, 4-(trifluoromethyl)-2-pyridyl-1-methyl, methoxy-4-pyridyl-methyl, methoxy-4-pyridyl-ethyl, dimethoxy-4-pyridyl-methyl, fluoro-4-pyridyl-methyl, difluoro-4-pyridyl-methyl, chloro-4-pyridyl-methyl, chloro-4-pyridyl-ethyl, dichloro-4-pyridyl-methyl, dichloro-4-pyridyl-methyl, bromo-4-pyridyl-methyl, dibromo-4-pyridyl-methyl, phenylmethyl (benzyl), phenylethyl, phenylpropyl, phenylbutyl, 2-methylphenylmethyl, 3-methylphenylmethyl, 4-methylphenylmethyl, 2-methylphenylethyl, 3-methylphenylethyl, 4-methylphenylethyl, 2,3-dimethylphenylmethyl, 2,4-dimethylphenylmethyl, 2,5-dimethylphenylmethyl, 2,6-dimethylphenylmethyl, 3,4-dimethylphenylmethyl, 3,5-dimethylphenylmethyl, 3,6-dimethylphenylmethyl, 2-ethylphenylmethyl, 3-ethylphenylmethyl, 4-ethylphenylmethyl, 2,3-diethylphenylmethyl, 2,4-diethylphenylmethyl, 2,5-diethylphenylmethyl, 2,6-diethylphenylmethyl, 3,4-diethylphenylmethyl, 3,5-diethylphenylmethyl, 3,6-diethylphenylmethyl, 2-trifluoromethyl-phenylmethyl, 3-trifluoromethyl-phenylmethyl, 4-trifluoromethyl-phenylmethyl, 2-trifluoromethyl-phenylethyl, 3-trifluoromethyl-phenylethyl, 4-trifluoromethyl-phenylethyl, 2,3-di-

trifluoromethyl-phenylmethyl, 2,4-di-trifluoromethyl-phenylmethyl, 2,5-di-trifluoromethyl-phenylmethyl, 2,6-di-trifluoromethyl-phenylmethyl, 3,4-di-trifluoromethyl-phenylmethyl, 3,5-di-trifluoromethyl-phenylmethyl, 3,6-di-trifluoromethyl-phenylmethyl, 2-methoxy-phenylmethyl, 3-methoxy-phenylmethyl, 4-methoxy-phenylmethyl, 2-methoxy-phenylethyl, 3-methoxy-phenylethyl, 4-methoxy-phenylethyl, dimethoxy-phenylmethyl, dimethoxy-phenylethyl, 2,4,6-trimethoxy-phenylmethyl, 2-ethoxy-phenylmethyl, 3-ethoxy-phenylmethyl, 4-ethoxy-phenylmethyl, ethoxy-phenylethyl, diethoxy-phenylmethyl, diethoxy-phenylethyl, 2,4,6-triethoxy-phenylmethyl, 2-fluorophenylmethyl, 3-fluorophenylmethyl, 4-fluorophenylmethyl, 2,3-difluorophenylmethyl, 2,4-difluorophenylmethyl, 2,5-difluorophenylmethyl, 2,6-difluorophenylmethyl, 3,4-difluorophenylmethyl, 3,5-difluorophenylmethyl, 3,6-difluorophenylmethyl, 2-fluorophenylethyl, 3-fluorophenylethyl or 4-fluorophenylethyl, 2-chlorophenylmethyl, 3-chlorophenylmethyl, 4-chlorophenylmethyl, 2,3-dichlorophenylmethyl, 2,4-dichlorophenylmethyl, 2,5-dichlorophenylmethyl, 2,6-dichlorophenylmethyl, 3,4-dichlorophenylmethyl, 3,5-dichlorophenylmethyl, 3,6-dichlorophenylmethyl, 2-chlorophenylethyl, 3-chlorophenylethyl, 4-chlorophenylethyl, 2-bromophenylmethyl, 3-bromophenylmethyl, 4-bromophenylmethyl, 2,3-dibromophenylmethyl, 2,4-dibromophenylmethyl, 2,5-dibromophenylmethyl, 2,6-dibromophenylmethyl, 3,4-dibromophenylmethyl, 3,5-dibromophenylmethyl, 3,6-dibromophenylmethyl, 2-bromophenylethyl, 3-bromophenylethyl or 4-bromophenylethyl. 2-phenyl-phenylmethyl, 3-phenyl-phenylmethyl, 4-phenyl-phenylmethyl, 2-phenoxy-phenylmethyl, 3-phenoxy-phenylmethyl, 4-phenoxy-phenylmethyl, 2-nitro-phenylmethyl, 3-nitro-phenylmethyl, 4-nitro-phenylmethyl, 2-amino-phenylmethyl, 3-amino-phenylmethyl, 4-amino-phenylmethyl, 2-dimethylamino-phenylmethyl, 3-dimethylamino-phenylmethyl, 4-dimethylamino-phenylmethyl, 2-cyano-phenylmethyl, 3-cyano-phenylmethyl, 4-cyano-phenylmethyl, 2-methanesulfonyl-phenylmethyl, 3-methanesulfonyl-phenylmethyl, 4-methanesulfonyl-phenylmethyl, 2-acid methyl ester-phenylmethyl, 3-acid methyl ester-phenylmethyl, 4-acid methyl ester-phenylmethyl, 2-thiazolyl-methyl, 4-thiazolyl-methyl, 5-thiazolyl-methyl, benzothiophenyl-2-methyl, 4-chloro-benzothiophenyl-2-methyl, 5-chloro-benzothiophenyl-2-methyl, 6-chloro-benzothiophenyl-2-methyl, 7-chloro-benzothiophenyl-2-methyl, benzothiophenyl-3-methyl, 4-chloro-benzothiophenyl-3-methyl, 5-chloro-benzothiophenyl-3-methyl, 6-chloro-benzothiophenyl-3-methyl, 7-chloro-benzothiophenyl-3-methyl, quinolinyl-2-methyl, quinolinyl-3-methyl, quinolinyl-6-methyl, 4-chloro-quinolinyl-6-methyl, 2-(trifluoromethyl)-quinolinyl-6-methyl, 4-chloro-2-(trifluoromethyl)-quinolinyl-6-methyl, 2-pyrimidyl, 4-pyrimidyl or 2[1,3,5-triazinyl].

Alkyl in R^1 is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms as defined above or substituted C_{1-7}-alkyl with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from heterocyclyl, aryl and cycloalkyl. Alkyl in R^1 is more preferable methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, 2-pyridylmethyl, 2-pyridylethyl, 2-pyridylpropyl, 2-pyridylbutyl, 3-pyridylmethyl, 3-pyridylethyl, 3-pyridylpropyl, 3-pyridylbutyl, 4-pyridylmethyl, 4-pyridylethyl, 4-pyridylpropyl, 4-pyridylbutyl, phenylmethyl (benzyl), cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-methoxy-phenylmethyl, 3-methoxy-phenylmethyl, 4-methoxy-phenylmethyl, 2,3-dimethoxy-phenylmethyl, 2,4-dimethoxy-phenylmethyl, 2,5-dimethoxy-phenylmethyl, 2,6-dimethoxy-phenylmethyl, 3,4-dimethoxy-phenylmethyl, 3,5-dimethoxy-phenylmethyl, 2,4,6-trimethoxy-phenylmethyl, 2-thiazolyl-methyl, 4-thiazolyl-methyl, 5-thiazolyl-methyl, benzothiophenyl-2-methyl, 4-chloro-benzothiophenyl-2-methyl, 5-chloro-benzothiophenyl-2-methyl, 6-chloro-benzothiophenyl-2-methyl, 7-chloro-benzothiophenyl-2-methyl, benzothiophenyl-3-methyl, 4-chloro-benzothiophenyl-3-methyl, 5-chloro-benzothiophenyl-3-methyl, 6-chloro-benzothiophenyl-3-methyl, 7-chloro-benzothiophenyl-3-methyl, quinolinyl-2-methyl, quinolinyl-3-methyl, quinolinyl-6-methyl, 4-chloro-quinolinyl-6-methyl, 2-(trifluoromethyl)-quinolinyl-6-methyl or 4-chloro-2-(trifluoromethyl)-quinolinyl-6-methyl, 2-(trifluoromethyl)-4-pyridyl-1-methyl, 3-(trifluoromethyl)-4-pyridyl-1-methyl, 2-(trifluoromethyl)-3-pyridyl-1-methyl, 4-(trifluoromethyl)-3-pyridyl-1-methyl, 3-(trifluoromethyl)-2-pyridyl-1-methyl, 4-(trifluoromethyl)-2-pyridyl-1-methyl or N-benzylamidomethyl. Further preferred alkyl substituents for R^1 are methyl, ethyl, isopropyl, cyclohexylmethyl, phenylmethyl or pyridylmethyl. Most preferred alkyl substituents for R^1 is 4-pyridylmethyl.

Alkyl in R^2 is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms as defined above, more preferable methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert.-butyl. Further preferred alkyl substituents for R^2 are methyl or n-propyl. Most preferred alkyl in R^2 is methyl.

Alkyl in R^3 is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms as defined above or substituted C_{1-7}-alkyl with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from heterocyclyl. More preferable alkyl in R^3 is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, 2-pyridylmethyl, 2-pyridylethyl, 3-pyridylmethyl, 3-pyridylethyl, 4-pyridylmethyl, 4-pyridylethyl. Further preferred alkyl substituents for R^3 are isopropyl, n-propyl or pyridylmethyl. Most preferred alkyl in R^3 is isopropyl. Alkyl in R^3 is not CF_3.

Alkyl in R^4 is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms as defined above or substituted C_{1-7}-alkyl (preferably C_{1-2}-alkyl) with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from hydroxy, amino, C_{1-4}-alkoxy (preferably, C_{1-2}-alkoxy), phenyl, methyl-oxy-carbonyl, ethyl-oxy-carbonyl, azido, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, methyl-sulfonyl-amino, phenyl-sulfonyl-amino, p-toluyl-sulfonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide. More preferred substituents for C_{1-7}-alkyl (preferably C_{1-2}-alkyl) are selected from hydroxy, amino, C_{1-2}-alkoxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide. Most preferred substituents for C_{1-7}-alkyl (preferably C_{1-2}-alkyl) are selected from hydroxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide. In case more than one substituent is attached to the alkyl group, these substituents can be identical or different from each other. Alkyl in R^4 is more preferable methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, 1,2-ethanediol, 1,2-propanediol, amino-methyl, amino-ethyl, methoxy-methyl, methoxy-ethyl, phenyl-methanol, (methyl-oxy-carbonyl)-(hydroxy-methyl), (ethyl-oxy-carbonyl)-(hydroxy-methyl), azido-methyl, azido-ethyl, 2-pyridyl-carbonyl-amino-methyl, 3-pyridyl-carbonyl-amino-methyl, 4-pyridyl-carbonyl-amino-methyl, (amino-methyl)-carbonyl-amino-methyl, (phenoxy)-carbonyl-amino-methyl, (methoxy)-carbonyl-amino-methyl, (di-methyl-amino)-carbonyl-amino-methyl, (phenyl-amino)-carbonyl-amino-methyl, (amino)-carbonyl-amino-methyl, (phenyl)-carbonyl-amino-methyl, (methyl)-carbonyl-amino-methyl, methyl-carbonyl-amino-methyl-carbonyl-amino-methyl, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino-methyl, (N1-acetyl-O-tert.-butyl-N2-ylmethyl)-L-serinamide,

(N1-acetyl-N2-yl]methyl)-L-serinamide, [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl-methyl]-L-serinamide, methyl-sulfonyl-amino-methyl, phenyl-sulfonyl-amino-methyl or p-toluyl-sulfonyl-amino-methyl. Preferred alkyl for R^4 is unsubstituted C_{1-7}-alkyl (preferably C_{1-4}-alkyl) or substituted C_{1-7}-alkyl (preferably C_{1-4}-alkyl, more preferred C_{1-2}-alkyl) with hydroxy or amino or methoxy as substituents. More preferable alkyl in R^4 is methyl or ethyl substituted with a hydroxy group or a methoxy group or (methyl)-carbonyl-amino-methyl. Further preferred alkyl groups for R^4 are methyl or ethyl substituted with a hydroxy group or a methoxy. More preferred alkyl in R^4 is methyl substituted with a hydroxy group or (methyl)-carbonyl-amino-methyl. Most preferred alkyl in R^4 is methyl substituted with a hydroxy group.

Alkyl in R^5 is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms (preferably, C_{1-4}-alkyl), as defined above or substituted C_{1-7}-alkyl (preferably C_{1-4}-alkyl, more preferred C_{1-2}-alkyl) with 1-3 substituents, preferably 1-2 substituents, more preferably 1 substituent selected from hydroxy, C_{1-4}-alkoxy (preferably methoxy or ethoxy), methyl-carbonyl-oxy or amino-carbonyl-oxy. Alkyl in R^5 is more preferable methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl, hydroxy-methyl, 1-hydroxy-ethyl, 2-hydroxy-ethyl, 1,2-ethanediol, 1,2-propanediol, methoxy-methyl, ethoxy-methyl, (methyl-carbonyl-oxy)-methyl, (amino-carbonyl-oxy)-methyl. More preferable alkyl in R^5 is methyl, ethyl, n-propyl, isopropyl or substituted C_{1-2}-alkyl substituted with 1-3 substituents selected from hydroxy, methyl-carbonyl-oxy and amino-carbonyl-oxy. Further preferred alkyl in R^5 is methyl, ethyl, (amino-carbonyl-oxy)-methyl or C_{1-2}-alkyl substituted with a hydroxy group. Another preferred alkyl in R^5 is methyl or (amino-carbonyl-oxy)-methyl, most preferred alkyl in R^5 is methyl.

In another preferred embodiment of the invention, alkyl in R^5 is unsubstituted alkyl or substituted alkyl with hydroxy as substituent, more preferably wherein alkyl in R^5 is methyl or ethyl optionally substituted with a hydroxy group, and most preferred wherein alkyl in R^5 is methyl.

Alkyl in R, R', R" and R"' is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms as defined above and more preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl.

Alkyl for N(alkyl) is preferably an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms and most preferred methyl.

The term "cycloalkyl" as used herein, and if not specified by the number of carbon atoms, denotes an optionally substituted cycloalkyl group containing 3 to 8 carbon atoms,

e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. The term "cycloalkyl" preferably denotes a cycloalkyl group containing 3 to 6 carbon atoms.

Suitable substituents for cycloalkyl can be selected from those named for alkyl, in addition however an oxo group (=O) can be added to the selection.

Cycloalkyl in R^1 and R^2 are as defined above.

Cycloalkyl in R^3 denotes an optionally substituted cycloalkyl group containing 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms. Most preferred cycloalkyl in R^3 denotes a cyclopropyl group.

The term "alkoxy" as used herein, and if not specified by the number of carbon atoms, denotes a straight or branched chain alkyl-oxy group wherein the "alkyl" portion is as defined above such as methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, tert.-butyloxy, pentyloxy, hexyloxy, heptyloxy including their different isomers. More preferred alkoxy groups within the invention are methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy or tert.-butyloxy.

Alkoxy in R is as defined above.

The term "alkenyl" as used herein, and if not specified by the number of carbon atoms, denotes an unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond, including their different isomers. Examples are vinyl or allyl.

Alkenyl in R^4 is as defined above.

The term "C(=O)R," as used herein for R^4, denotes a hydrogen atom, an C_{1-7}-alkyl group (preferably C_{1-4}-alkyl as defined above for the alkyl substituent R), alkoxy (preferably C_{1-4}-alkoxy), trifluoromethyl, methyl-oxy-carbonyl, ethyl-oxy-carbonyl, each of these substituents attached to a keto function -C(=O)-. Preferred examples are an aldehyde group (C(=O)H), methyl-carbonyl, ethyl-carbonyl, tert.-butoxy-carbonyl, trifluoromethyl-carbonyl, methyl-oxy-dicarbonyl or ethyl-oxy-carbonyl.

The term " CONR'R" " as used herein for R^4, denotes, independently of each other, hydrogen, C_{1-7}-alkyl (preferably C_{1-4}-alkyl), substituted aryl (preferably phenyl), each of these substituents attached to a amino-carbonyl function. Preferred examples are amino-carbonyl ($CONH_2$), (methyl-amino)-carbonyl, (dimethyl-amino)-carbonyl, (phenyl-amino)-carbonylv or (2,4,6-trimethoxy-methyl)-amino-carbonyl.

The term " -Z-C(=O)R''' " as used herein for R^5, wherein Z is a single bond or -CH=CH- and R''' is hydrogen or alkyl (preferably C_{1-4}-alkyl) denotes an aldehyde group (C(=O)H), methyl-carbonyl or ethyl-carbonyl, aldehyde-ethylene (-CH=CH)C(=O)H), (methyl-carbonyl)-ethylene (-CH=CH)C(=O)CH_3) or (ethyl-carbonyl)-ethylene (-CH=CH)C(=O)C_2H_5). The ethylene group of the invention can have the (E) or (Z) configuration. Both isomeric forms of these compounds are embraced by the present invention.

The term "aryl" as used herein denotes an optionally substituted phenyl and naphthyl, both optionally benz-fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic, bicyclic or tricyclic heterocycle or carbocycle e.g. to cyclohexyl or cyclopentyl.

Suitable substituents for aryl can be selected from those named for alkyl, in addition however C_{1-4}-alkyl, trifluoromethyl, trifluoromethoxy, C_{2-4}-alkenyl, 1,2-propanediol, cyano and hydroxy-methyl can be added to the selection.

In case more than one substituent is attached to the aryl group, these substituents can be identical or different from each other.

Aryl in R^1 is preferably an unsubstituted or substituted phenyl with suitable substituents selected from 1 to 5 of halogen, nitro and unsubstituted straight or branched chain alkyl containing 1 to 4 carbon atoms.

Aryl in R^2 is preferably an unsubstituted or substituted phenyl or naphthyl (preferably phenyl) with suitable substituents selected from 1 to 5 substituents, preferably 1-4 substituents, more preferably 1-3 substituent selected from C_{1-7}-alkyl (preferable C_{1-4}-alkyl), trifluoromethyl, C_{1-4}-alkoxy (preferable C_{1-2}-alkoxy), trifluoromethoxy, C_{2-4}-alkenyl, 1,2-propanediol, fluorine, chlorine, bromine, iodine, nitro, cyano, phenyl, hydroxy-methyl, 4-pyridyl, 3-pyridyl and 2-pyridyl (preferably 1-3 substituent selected from C_{1-7}-alkyl (preferable C_{1-4}-alkyl), halogen and nitro; more preferably 1-3 substituent selected from halogen; most preferably 1-3 substituent selected from chlorine). In case more than one substituent is attached to the aryl group, these substituents can be identical or different from each other. Examples of substituted aryl groups are 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2-ethyl-phenyl, 3-ethyl-phenyl, 4-ethyl-phenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethylphenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 3,6-dimethylphenyl, 2,4,6-trimethylphenyl, 3,4,5-trimethylphenyl, 2,3,4-trimethylphenyl, 2,4,5-trimethylphenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl, 2,5-dimethoxy-phenyl, 2,6-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,5-dimethoxy-

phenyl, 3,6-dimethoxy-phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3,6-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,6-dichlorophenyl, 2,4,6-trichlorophenyl, 3,4,5-trichlorophenyl, 2,3,4-trichlorophenyl, 2,4,5-trichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 3,6-dibromophenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl, 4-trifluoromethyl-phenyl, 2-cyano-phenyl, 3-cyano-phenyl, 4-cyano-phenyl, 2,3-di-cyano-phenyl, 2,4-di-cyano-phenyl, 2,5-di-cyano-phenyl, 2,6-di-cyano-phenyl, 3,4-di-cyano-phenyl, 3,5-di-cyano-phenyl, 3,6-di-cyano-phenyl, 2-nitro-phenyl, 3-nitro-phenyl, 4-nitro-phenyl, 2-(trifluoromethoxy)phenyl, 3-(trifluoromethoxy)phenyl, 4-(trifluoromethoxy)phenyl, 2-(phenyl)phenyl, 3-(phenyl)phenyl, 4-(phenyl)phenyl, 2-(hydroxymethyl)phenyl, 3-(hydroxymethyl)phenyl, 4-(hydroxymethyl)phenyl, 2-(2-pyridyl)phenyl, 3-(2-pyridyl)phenyl, 4-(2-pyridyl)phenyl, 2-(3-pyridyl)phenyl, 3-(3-pyridyl)phenyl, 4-(3-pyridyl)phenyl, 2-(4-pyridyl)phenyl, 3-(4-pyridyl)phenyl, 4-(4-pyridyl)phenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-methyl-phenyl, 3-chloro-5-bromo-phenyl, 3-chloro-5-propyl-phenyl, 3-chloro-5-methyl-phenyl, 3-chloro-5-ethyl-phenyl, 3-chloro-5-vinyl-phenyl, 3-chloro-5-allyl-phenyl, 3-chloro-5-phenyl-phenyl, 3-chloro-5-(hydroxymethyl)-phenyl, 3-chloro-5-cyano-phenyl, 3-chloro-5-(1,2-propanediol)-phenyl, 2-naphthyl or 3-cyano-5-methyl. Preferred example for aryl in R^2 is 3,5-dichlorophenyl.

Aryl in R^3 is preferably an unsubstituted or substituted phenyl with suitable substituents selected from 1 to 5 substituents, preferably 1-4 substituents, more preferably 1-3 substituent selected from C_{1-4}-alkyl (preferable C_{1-2}-alkyl), C_{1-4}-alkoxy (preferable C_{1-2}-alkoxy), fluorine, chlorine, bromine, iodine and phenyl (preferably 1-3 substituent selected from C_{1-4}-alkyl (preferable C_{1-2}-alkyl), C_{1-4}-alkoxy (preferable C_{1-2}-alkoxy) and halogen; more preferably 1-3 substituent selected from C_{1-4}-alkyl (preferable C_{1-2}-alkyl) and C_{1-4}-alkoxy (preferable C_{1-2}-alkoxy). Examples of substituted aryl groups are 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl or 3,6-dichlorophenyl. Most preferred aryl in R^3 is phenyl.

Aryl in R^5, R' and R'' is as defined above, preferably phenyl.

The term "heterocyclyl" as used herein denotes an optionally substituted saturated, partially unsaturated or aromatic monocyclic or bicyclic heterocycle which contains 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur which can also be fused to an optionally substituted saturated, partially unsaturated or aromatic monocyclic carbocycle or heterocycle.

Examples of suitable heterocycles are oxazolyl, isoxazolyl, furyl, tetrahydrofuryl, 1,3-dioxolanyl, dihydropyranyl, thienyl, pyrazinyl, isothiazolyl, isoquinolinyl, indolyl, indazolyl, quinolinyl, dihydrooxazolyl, pyrimidinyl, benzofuranyl, tetrazolyl, pyrrolidinyl, pyrrolidinonyl, (N-oxide)-pyridinyl, pyrrolyl, triazolyl e.g. 1,2,4-triazolyl, pyrazolyl, benzotriazolyl, piperidinyl, morpholinyl, thiazolyl, pyridyl, dihydrothiazolyl, imidazolidinyl, pyrazolinyl, benzothienyl, piperazinyl, imidazolyl, thiadiazolyl e.g. 1,2,3-thiadiazolyl, and benzothiazolyl. Most preferred example is pyridyl.

Heterocyclyl in R^1, R^2 and R^3 are preferably an unsubstituted or substituted pyridyl with suitable substituents selected from 1 to 5 of halogen, nitro and unsubstituted straight or branched chain alkyl containing 1 to 4 carbon atoms.

Suitable substituents for heterocyclyl can be selected from those named for alkyl, in addition however an oxo group (=O) as substituent can be added to the selection.

The term " C(=O)R ", as used herein denotes an carbonyl group to which the following substituents are attached, wherein the substituents selected from hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl and ethyl-oxy-carbonyl (preferably hydrogen or alkyl). Examples for suitable substituents for the carbonyl group are hydrogen, tert.-butoxy, trifluoromethyl, methyl, ethyl-oxy-carbonyl. In an other embodiment of the invention preferred acyl groups are those wherein R is hydrogen or an unsubstituted straight or branched chain hydrocarbon residue containing 1 to 7 carbon atoms.

The term " CONR'R" " as used herein denotes amides wherein R' and R", are independently of each other, hydrogen, alkyl or aryl (preferably hydrogen or C_{1-7}-alkyl (preferable C_{1-4}-alkyl)). Examples for suitable substituents for the amide group (R' and/or R") are hydrogen, C_{1-4}-alkyl (preferably methyl), phenyl, 2,4,6-trimethoxy-benzyl.

Within the invention the term "X" represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together represent CH_2-aryl (preferably CH_2-phenyl) or CH_2-heterocyclyl (preferably CH_2-(4)-pyridyl, CH_2-(3)-pyridyl, CH_2-(2)-pyridyl), more preferable S, S(O), $S(O)_2$, O, N(alkyl) and most preferred the term "X" represents S.

The term halogen stands for fluorine, chlorine, bromine and iodine. Most preferred halogen is chlorine.

Any functional (i.e. reactive) group present in a side-chain may be protected, with the protecting group being a group which is known per se, for example, as described in "Protective Groups in Organic Synthesis", 2nd Ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1991. For example, an amino group can be protected by tert.-butoxycarbonyl (BOC) or benzyloxycarbonyl (Z).

The compounds of this invention may contain one or more asymmetric carbon atoms and may therefore occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Furthermore, where a compound of the invention contains an olefinic double bond, this can have the (E) or (Z) configuration. Also, each chiral center may be of the R or S configuration. All such isomeric forms of these compounds are embraced by the present invention.

Compounds of formula I which are acidic can form pharmaceutically acceptable salts with bases such as alkali metal hydroxides, e.g. sodium hydroxide and potassium hydroxide; alkaline earth metal hydroxides, e.g. calcium hydroxide, barium hydroxide and magnesium hydroxide, and the like; with organic bases e.g. N-ethyl piperidine, dibenzylamine, and the like. Those compounds of formula (I) which are basic can form pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric acid and hydrobromic acid, sulphuric acid, nitric acid and phosphoric acid, and the like, and with organic acids, e.g. with acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid and p-toluene sulphonic acid, and the like. The formation and isolation of such salts can be carried out according to methods known in the art.

A preferred embodiment of the invention are compounds of formula I wherein

R^1 is alkyl,

preferably wherein

R^1 is C_{1-7} alkyl or C_{1-7} alkyl substituted with 1-3 substituents selected from cycloalkyl, aryl and heterocyclyl,

more preferably wherein

R^1 is methyl, ethyl, isopropyl, cyclohexylmethyl, phenylmethyl, pyridylmethyl,

most preferably wherein

R^1 is 4-pyridylmethyl;

R^2 is alkyl or aryl,

preferably wherein

R^2 is C_{1-7} alkyl, phenyl or phenyl substituted with 1-5 substituents selected from C_{1-7} alkyl, halogen and nitro,

more preferably wherein

R^2 is methyl, n-propyl or phenyl substituted with 1-5 chlorine atoms,

most preferably wherein

R^2 is methyl or 3,5-dichlorophenyl;

R^3 is alkyl, cycloalkyl or aryl,

preferably wherein

R^3 is C_{1-7} alkyl, C_{1-7} alkyl substituted with 1-3 heterocyclyl, phenyl or phenyl substituted with 1-5 substituents selected from C_{1-4}-alkyl, C_{1-4}-alkoxy and halogen;

more preferably wherein

R^3 is isopropyl, n-propyl or pyridylmethyl,

most preferably wherein

R^3 is isopropyl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R, CONR'R", cyano or alkenyl, wherein

R is hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl, wherein

R' and R", are independently of each other, hydrogen, alkyl or aryl,

preferably wherein

R^4 is hydrogen, C_{1-7} alkyl or C_{1-7} alkyl substituted with 1-3 substituents selected from hydroxy, amino, C_{1-4}-alkoxy, phenyl, methyl-oxy-carbonyl, ethyl-oxy-carbonyl, azido, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, methyl-sulfonyl-amino, phenyl-sulfonyl-amino, p-toluyl-sulfonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide,

more preferably wherein

R^4 is hydrogen or C_{1-2} alkyl substituted with 1-3 substituents selected from hydroxy, amino, C_{1-2}-alkoxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide,

most preferably wherein

R^4 is C_{1-2} alkyl substituted with 1-2 substituents selected from hydroxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide;

R^5 is alkyl, aryl or a group -Z-C(=O)R'", wherein

Z is a single bond or –CH=CH-, and

R'" is hydrogen or alkyl,

preferably wherein

R^5 is C_{1-7} alkyl, phenyl, C_{1-7} alkyl substituted with 1-3 substituents selected from hydroxy, C_{1-4}-alkoxy, methyl-carbonyl-oxy and amino-carbonyl-oxy,

more preferably wherein

R^5 is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl or C_{1-2}-alkyl substituted with 1-3 substituents selected from hydroxy, C_{1-2}-alkoxy, methyl-carbonyl-oxy and amino-carbonyl-oxy,

most preferably wherein

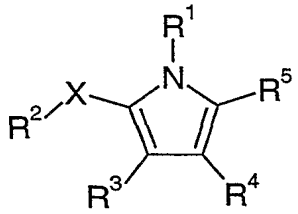
R^5 is methyl, ethyl, n-propyl, isopropyl or C_{1-2}-alkyl substituted with 1-3 substituents selected from hydroxy, methyl-carbonyl-oxy and amino-carbonyl-oxy;

X represents S, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that alkyl in R^3 is not CF_3,

preferably wherein

X represents S.

Other preferred embodiments of the invention are compounds of formula I wherein



I

R^1 is alkyl, cycloalkyl, aryl or heterocyclyl,

preferably wherein

R^1 is alkyl,

more preferably wherein

R^1 is alkyl substituted with heterocyclyl or aryl, unsubstituted C_{1-7} alkyl or alkyl substituted with cycloalkyl,

most preferably wherein

R^1 is pyridylmethyl, phenylmethyl, methyl, ethyl, isopropyl, cyclohexylmethyl;

R^2 is alkyl, cycloalkyl, aryl or heterocyclyl,

preferably wherein

R^2 is alkyl or aryl,

more preferably wherein

R^2 is unsubstituted alkyl, unsubstituted phenyl or substituted phenyl with 1 to 5 halogen or nitro or unsubstituted C_{1-7} alkyl as substituents,

most preferably wherein

R^2 is methyl, n-propyl or chlorinated phenyl;

R^3 is hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl,

preferably wherein

R^3 is alkyl or aryl,

more preferably wherein

R^3 is unsubstituted alkyl or substituted alkyl with heterocyclyl as substituent, unsubstituted phenyl or substituted phenyl with 1 to 5 halogen or methoxy or unsubstituted alkyl as substituents,

most preferably wherein

R^3 is isopropyl, n-propyl or pyridylmethyl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R or $CONR_2$ wherein

R is hydrogen or alkyl,

preferably wherein

R^4 is hydrogen, alkyl, carboxyl, C(=O)R or $CONR_2$,

more preferably wherein

R^4 is hydrogen, unsubstituted alkyl or substituted alkyl with hydroxy or amino or methoxy as substituents, carboxyl, C(=O)R, $CONR_2$,

most preferably wherein

R^4 is methyl or ethyl with hydroxy or methoxy as substituents, carboxyl, C(=O)R, $CONR_2$;

R^5 is hydrogen or alkyl,

preferably wherein

R^5 is hydrogen, unsubstituted alkyl or substituted alkyl with hydroxy as substituent,

more preferably wherein

R^5 is methyl or ethyl optionally substituted with a hydroxy group;

X represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that

only one of R^3, R^4 and R^5 is hydrogen and alkyl in R^3 is not CF_3,

preferably wherein

X represents S, S(O), $S(O)_2$, O, N(alkyl),

more preferably wherein

X represents S;

hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof.

Other preferred embodiments of the invention are compounds of formula I wherein

R^1 is 4-pyridyl methyl;

R^2 is methyl or 3,5-dichlorophenyl;

R^3 is isopropyl;

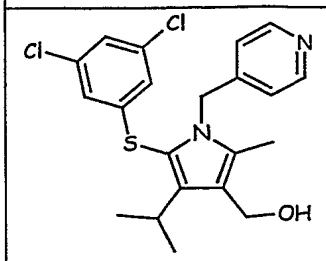
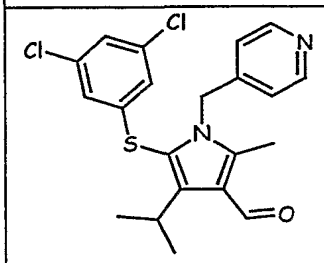
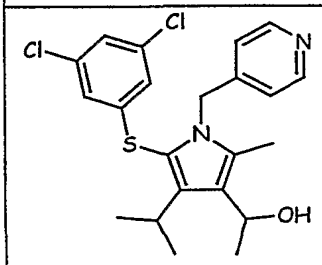
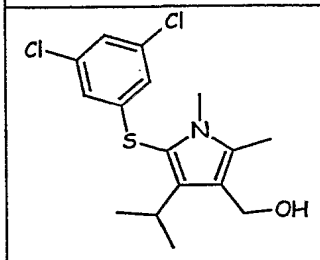
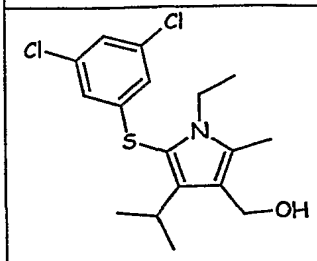
R^4 is methyl substituted with a hydroxy group or C(=O)R;

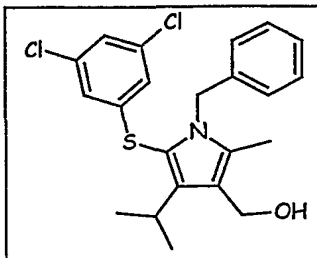
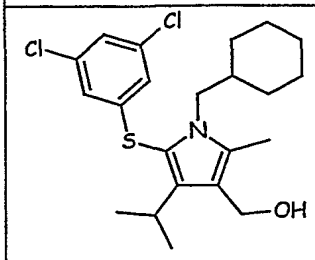
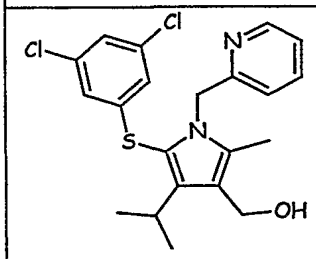
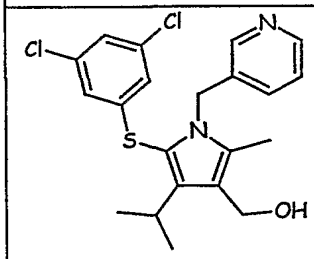
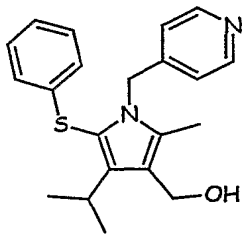
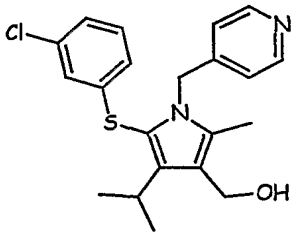
R^5 is methyl;

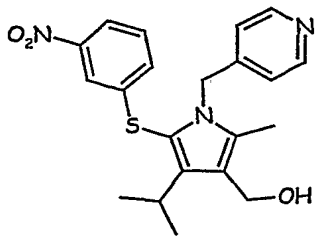
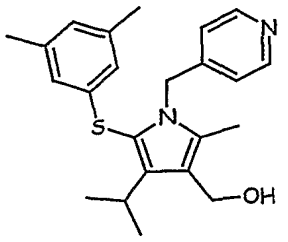
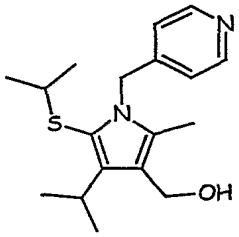
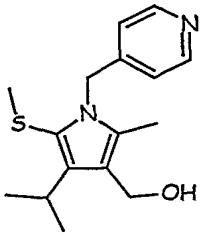
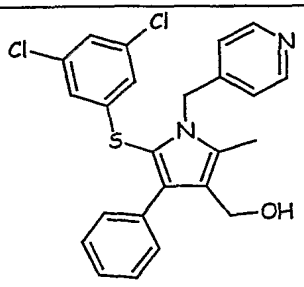
X represents S.

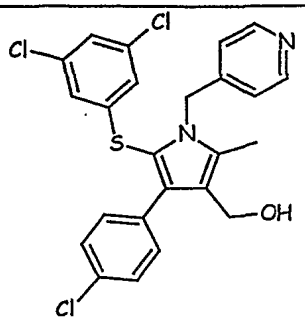
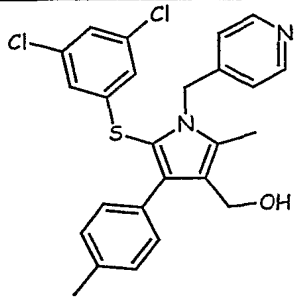
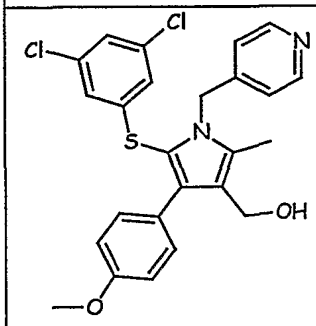
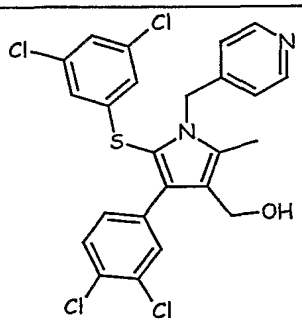
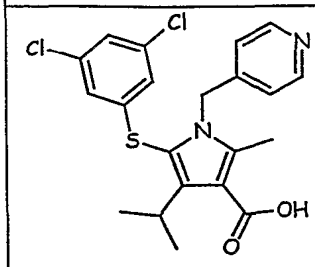
More preferred embodiments of compounds of formula I, as well as hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof, are listed in table 1 (see below):

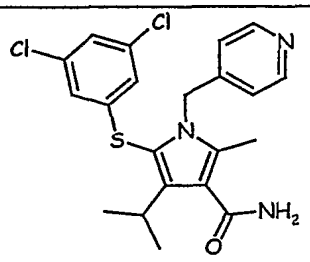
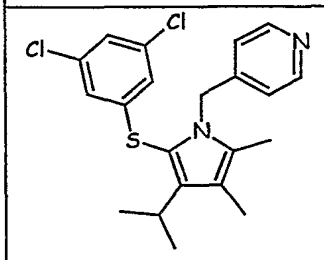
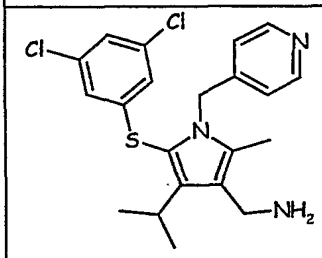
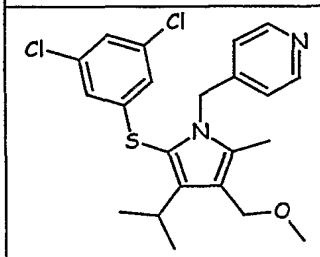
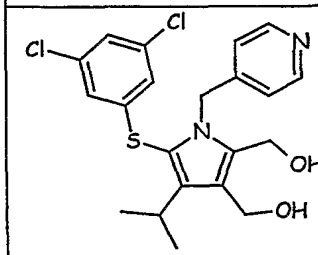
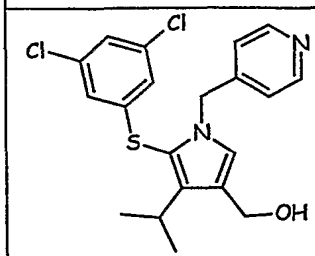
Table 1

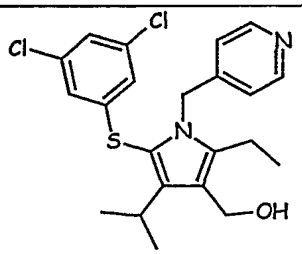
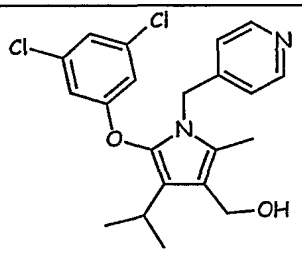
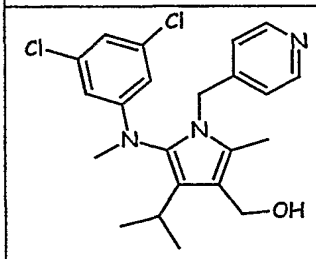
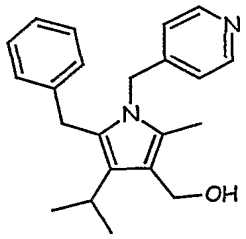
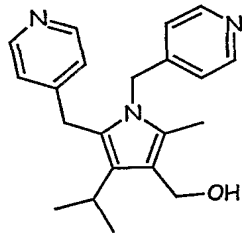
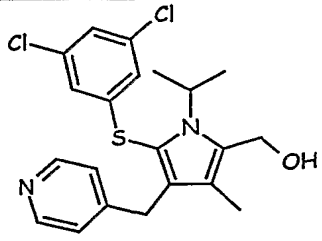
STRUCTURE	SYSTEMATIC NAME
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxaldehyde
	5-(3,5-Dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1,2-dimethyl-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-1-ethyl-4-isopropyl-2-methyl-1H-pyrrole-3-methanol

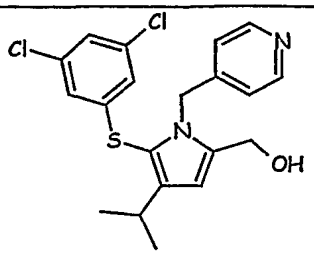
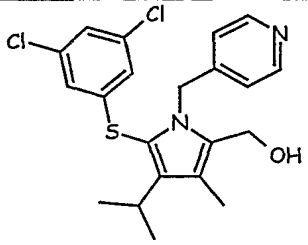
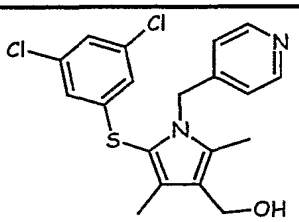
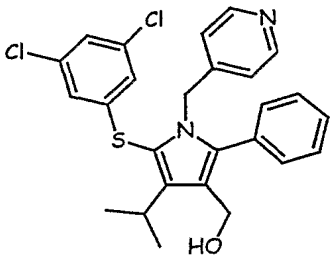
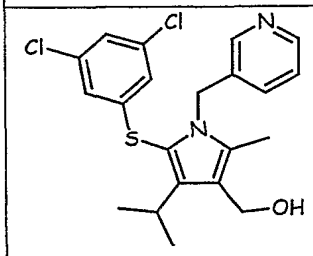
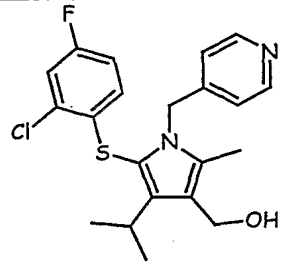
	1-Benzyl-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol
	1-(Cyclohexylmethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(2-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-phenylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

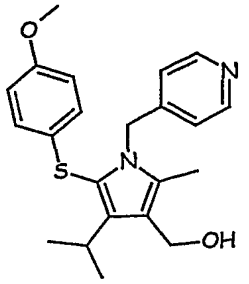
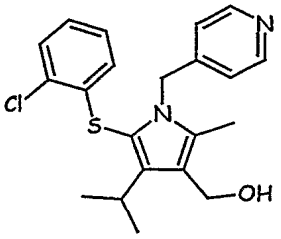
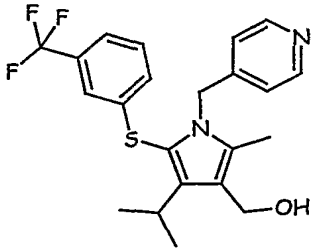
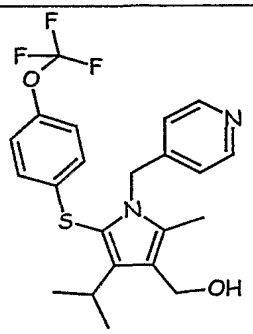
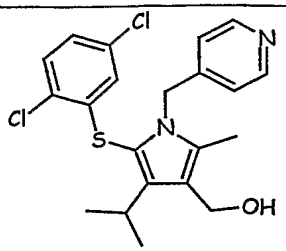
	4-Isopropyl-2-methyl-5-(3-nitrophenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dimethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-5-isopropylthio-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-methylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

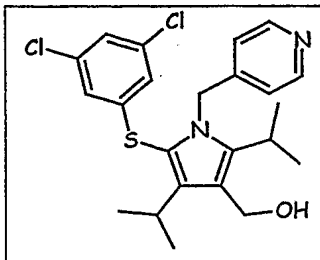
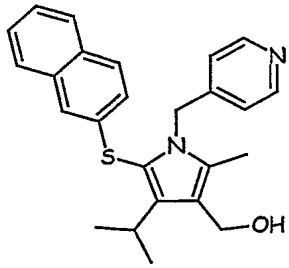
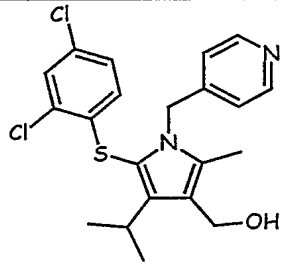
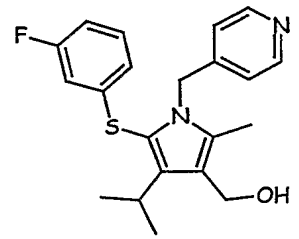
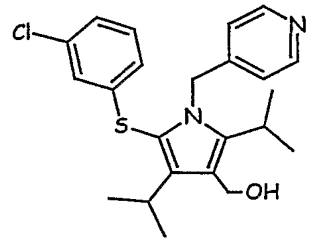
	4-(4-Chlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-2-methyl-4-(4-methylphenyl)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-(4-methoxyphenyl)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-(3,4-Dichlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid

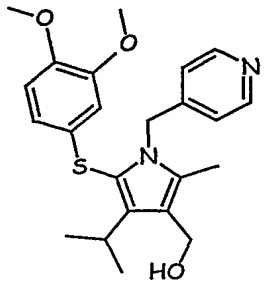
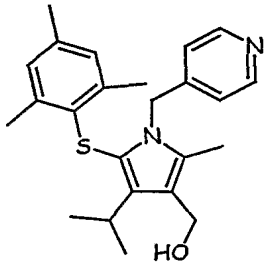
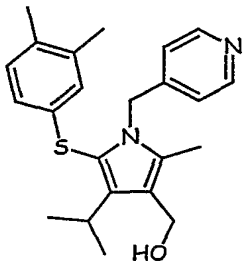
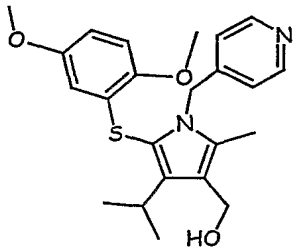
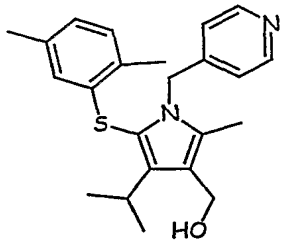
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4,5-dimethyl-1H-pyrrol-1-yl]methyl]pyridine
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylamine
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1H-pyrrol-1-yl]methyl]pyridine
	5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

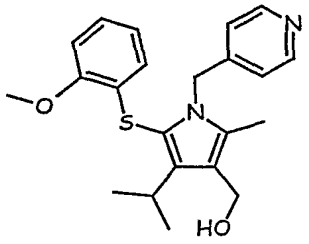
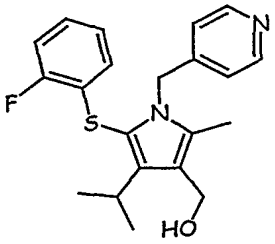
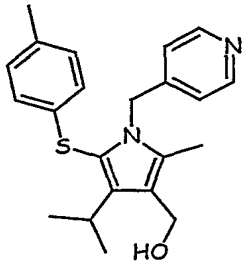
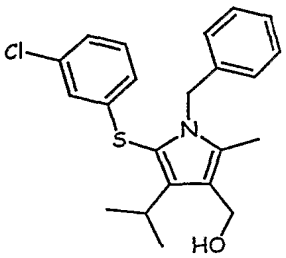
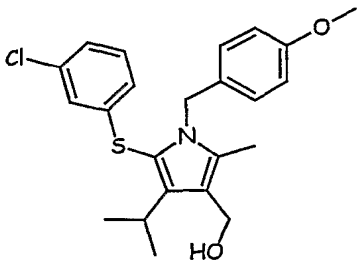
	5-(3,5-Dichlorophenylthio)-2-ethyl-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenoxy)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-[(3,5-Dichlorophenyl)methylamino]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-Benzyl-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-1,5-bis[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-1-isopropyl-3-methyl-4-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol

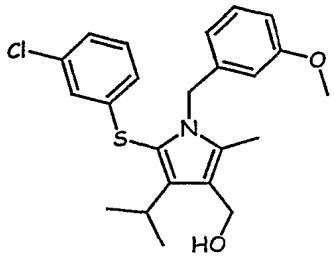
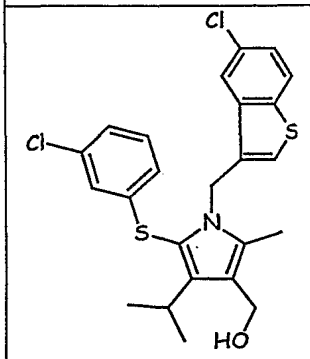
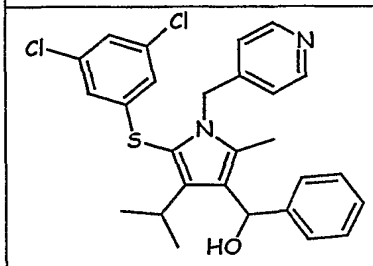
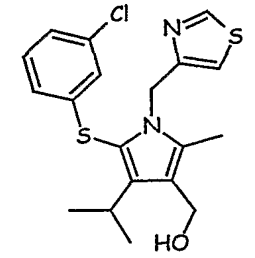
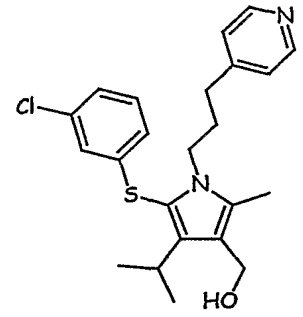
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-3-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol
	5-(3,5-Dichlorophenylthio)-2,4-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2-chloro-4-fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

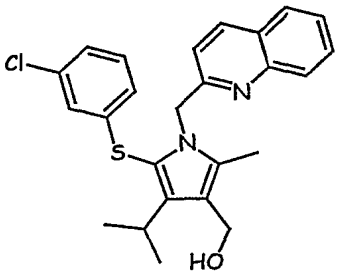
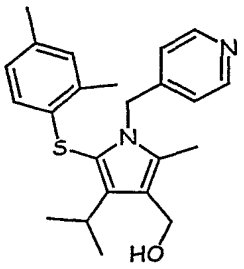
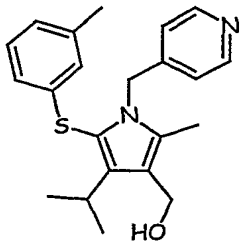
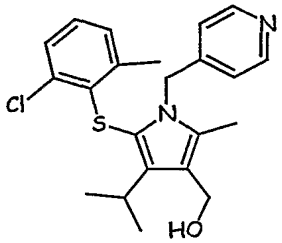
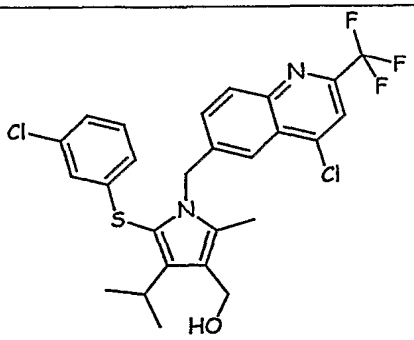
	4-Isopropyl-5-(4-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-[3-(Trifluoromethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-[4-(Trifluoromethoxy)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

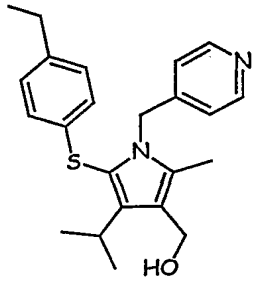
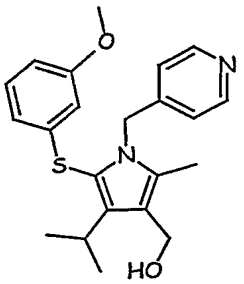
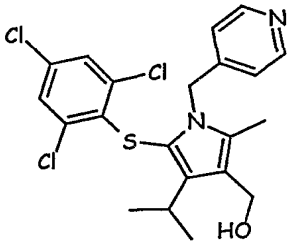
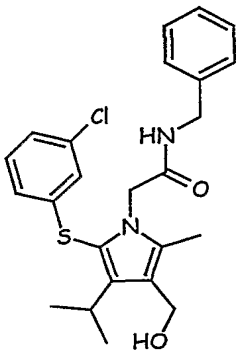
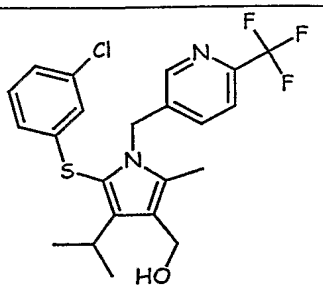
	5-(3,5-Dichlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(2-naphthylthio)-1[(4-pyridinyl)methyl]-1H-pyrrole-3-methanol
	5-(2,4-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3-Chlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

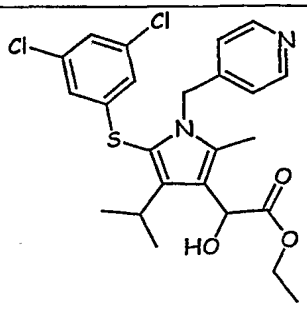
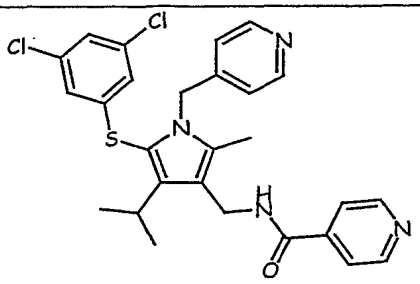
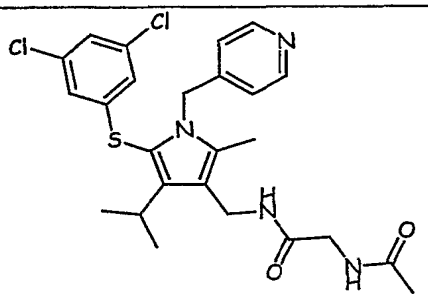
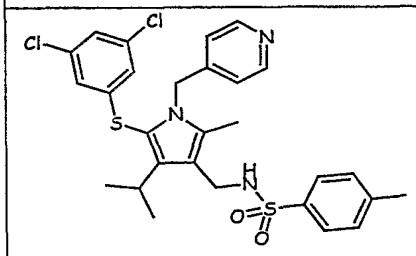
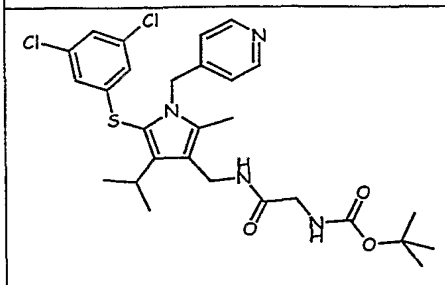
	4-Isopropyl-5-(3,4-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(2,4,6-trimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(3,4-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-5-(2,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(2,5-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

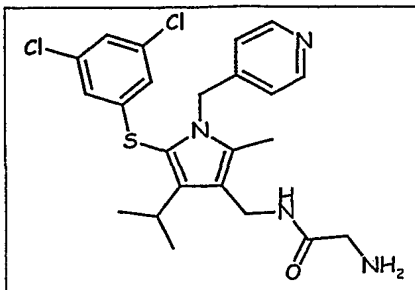
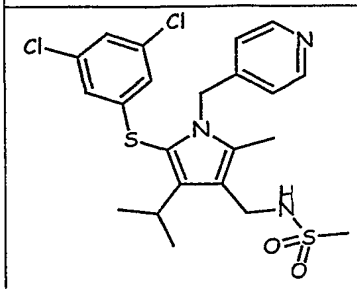
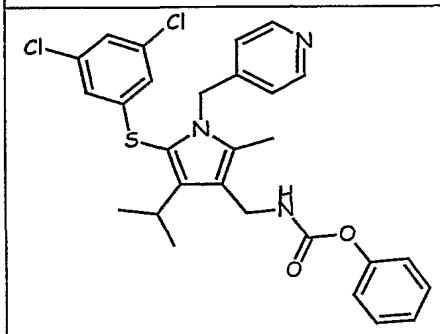
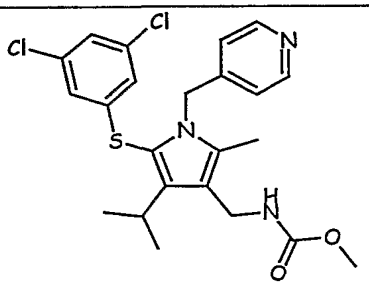
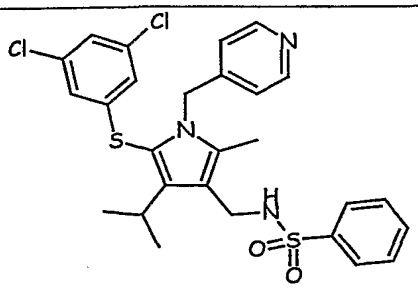
	4-Isopropyl-5-(2-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(4-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	1-Benzyl-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol
	5-(3-Chlorophenylthio)-4-isopropyl-1-(4-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol

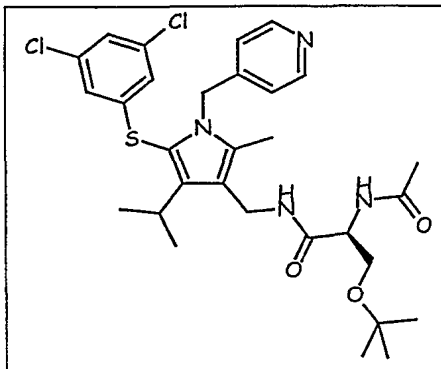
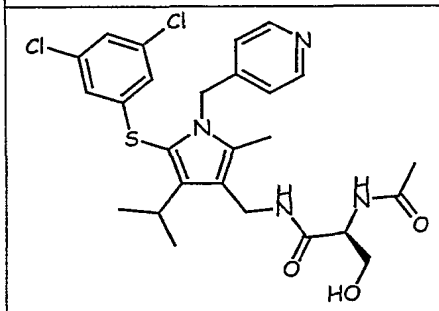
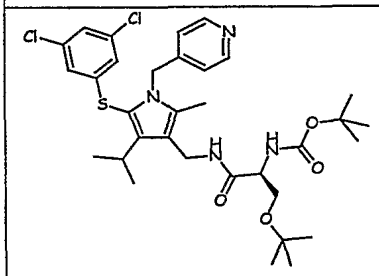
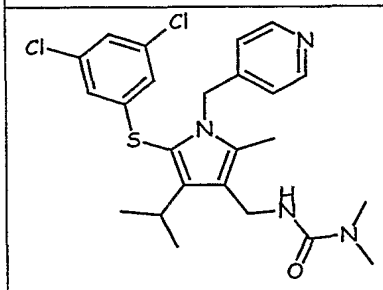
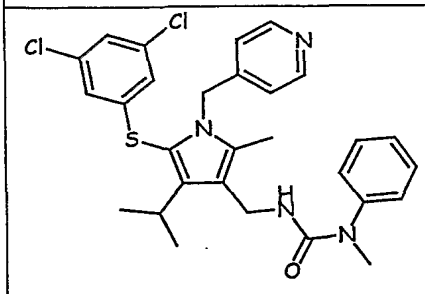
	5-(3-Chlorophenylthio)-4-isopropyl-1-(3-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol
	1-[(5-Chloro-1-benzothiophen-3-yl)methyl]-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol
	alpha(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]benzyl alcohol
	5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-thiazolyl)methyl]-1H-pyrrole-3-methanol
	5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(3-(4-pyridyl)propyl]-1H-pyrrole-3-methanol

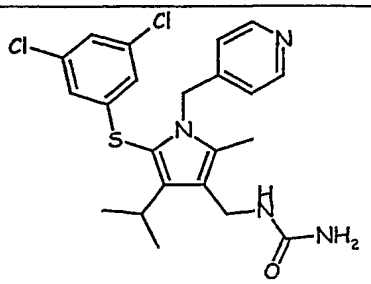
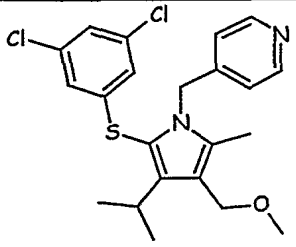
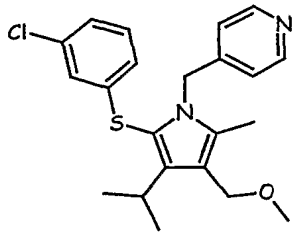
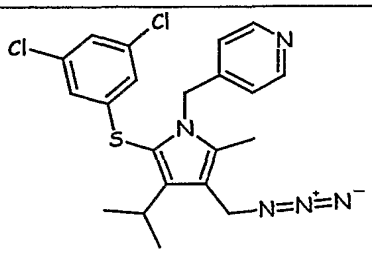
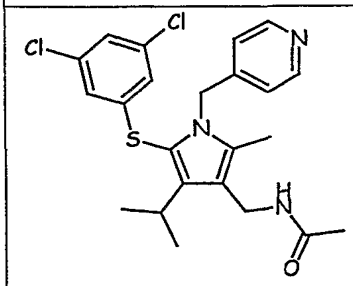
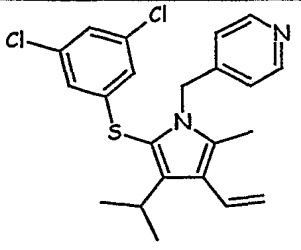
	5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(2-quinolyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(2,4-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-5-(3-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2-Chloro-6-methylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(3-Chlorophenylthio)-1-[[4-chloro-2-(trifluoromethyl)-6-quinolyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol

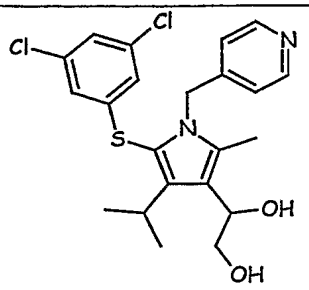
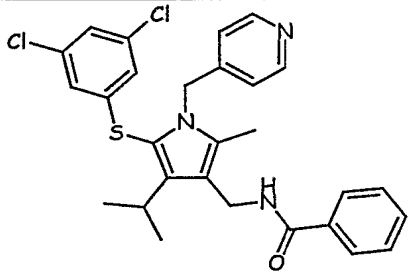
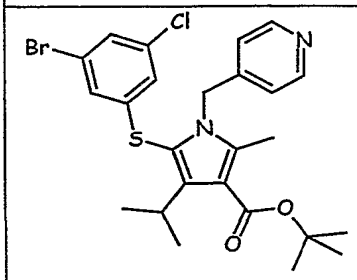
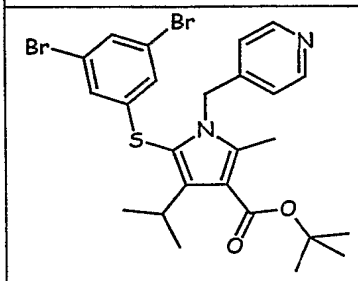
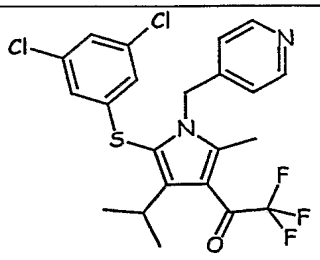
	5-(4-Ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-5-(3-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(2,4,6-Trichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	N-Benzyl-2-(3-chlorophenylthio)-4-(hydroxymethyl)-3-isopropyl-5-methyl-1-pyrroleacetamide
	5-(3-Chlorophenylthio)-1-[[6-(trifluoromethyl)-3-pyridyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol

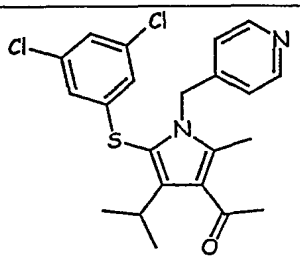
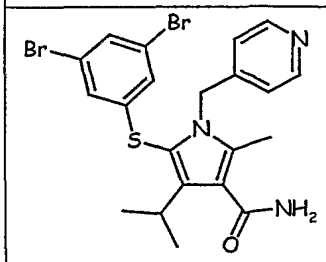
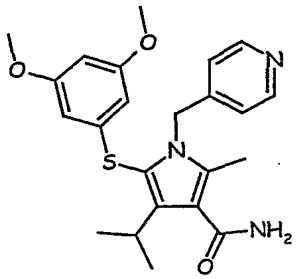
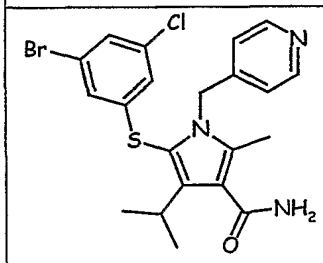
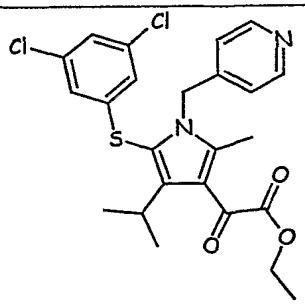
	[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-2-methyl-1-pyridin-4-ylmethyl-1H-pyrrol-3-yl]-hydroxy-acetic acid ethyl ester
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-4-pyridineacetamide
	2-Acetamido-N-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-p-toluenesulfonamide
	tert.-butyl [[[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamoyl]methyl]carbamate

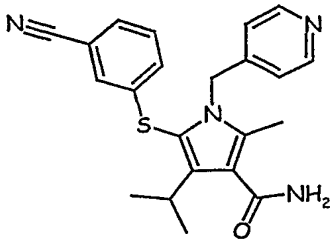
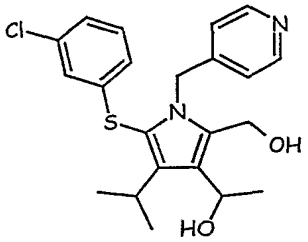
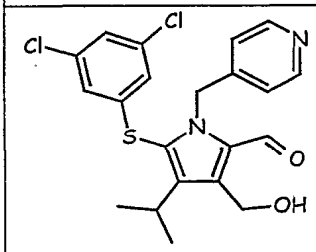
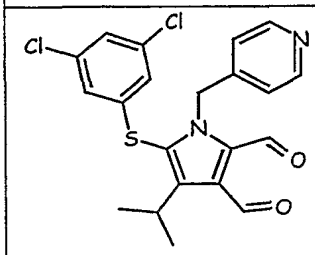
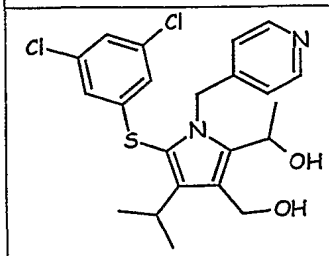
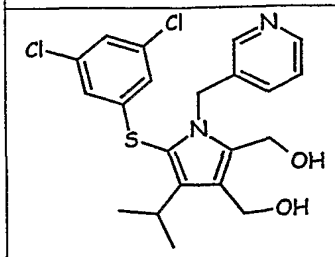
	N2-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]glycinamide
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl-1H-pyrrol-3-yl]methyl]methanesulfonamide
	Phenyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate
	Methyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzenesulfonamide

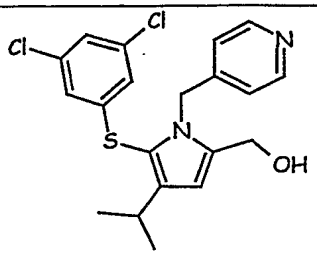
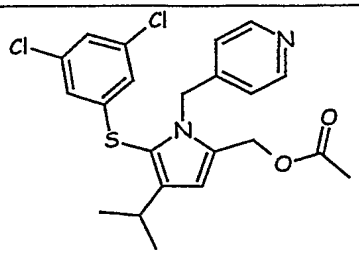
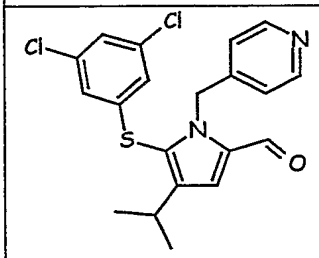
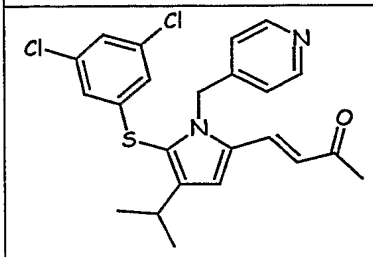
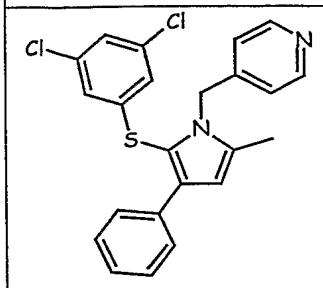
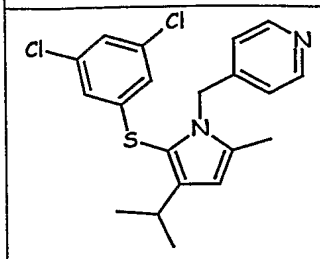
 Chiral	N1-acetyl-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-ylmethyl]-L-serinamide
 Chiral	N1-acetyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide
 Chiral	N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide
	1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-3,3-dimethylurea
	1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyriyl)methyl]-1H-pyrrol-3-yl]methyl]-3-methyl-3-phenylurea

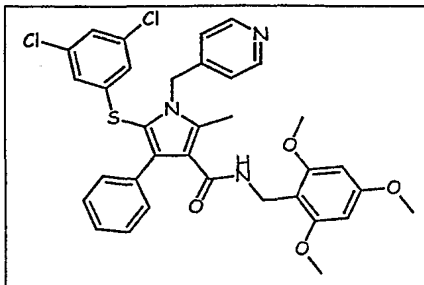
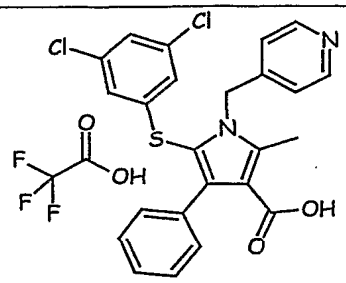
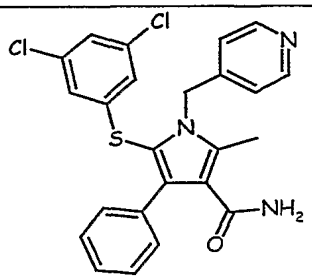
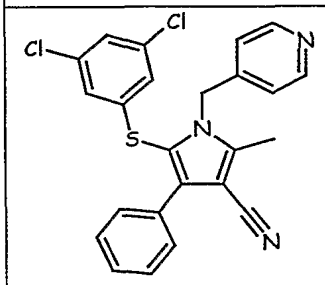
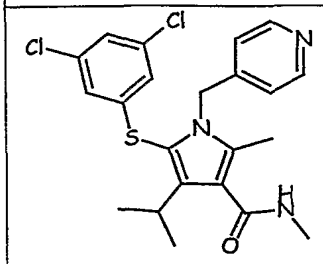
	1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]urea
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine
	4-[[2-(3-Chlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine
	4-[[3-(Azidomethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridine
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-4-vinyl-1-pyrrolyl]methyl]pyridine

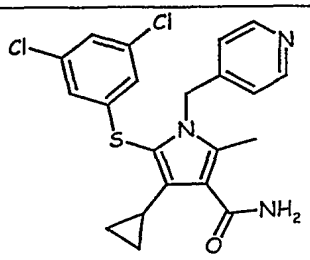
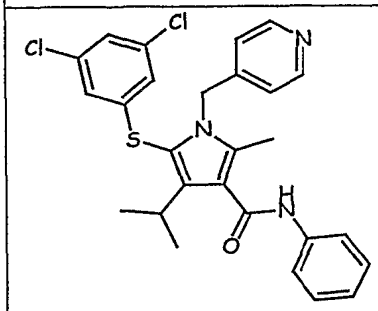
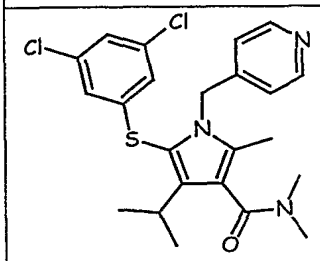
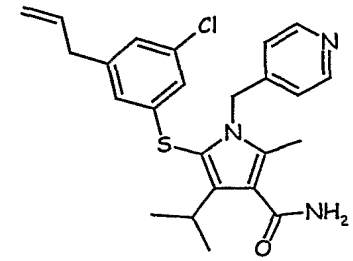
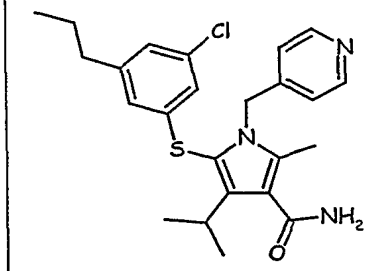
	1(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-1,2-ethanediol
	N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzamide
	tert.-butyl 5-(3-bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate
	tert.-butyl 5-(3,5-dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate
	1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-2,2,2-trifluoroethanone

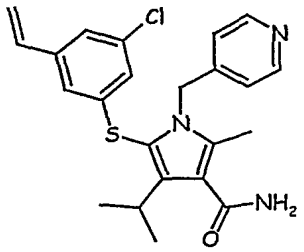
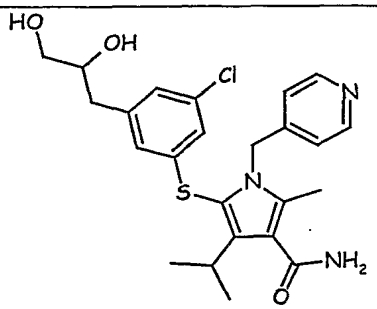
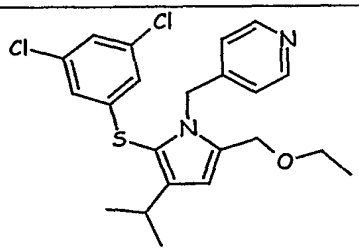
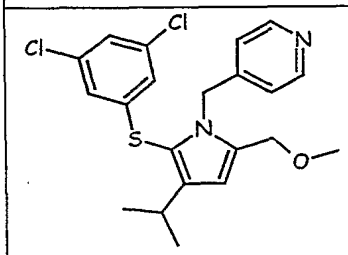
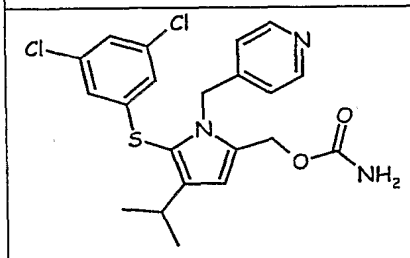
	1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]ethanone
	5-(3,5-Dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	4-Isopropyl-5-(3,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3-Bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	Ethyl 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-glyoxalate

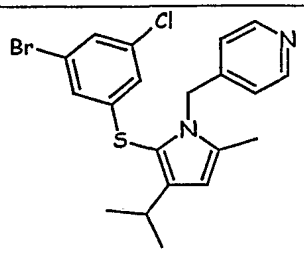
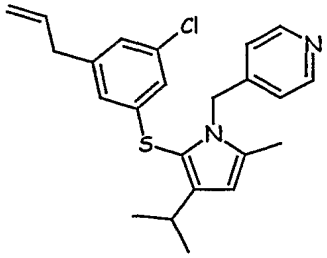
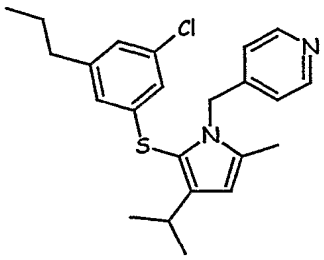
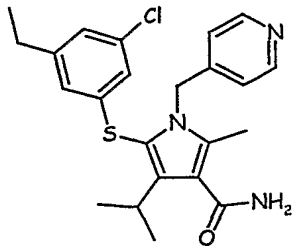
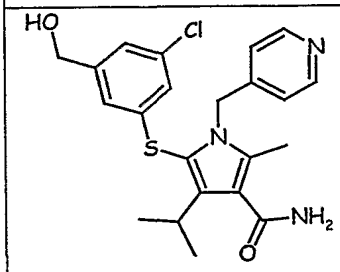
	5-(3-Cyanophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3-Chlorophenylthio)-2-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol
	5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehyde
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-dicarboxaldehyde
	5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-ethanol
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(3-pyridyl]methyl]-1H-pyrrole-2,3-dimethanol

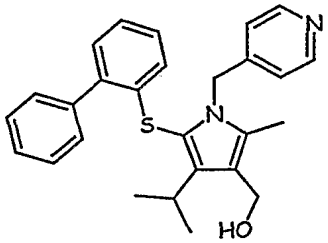
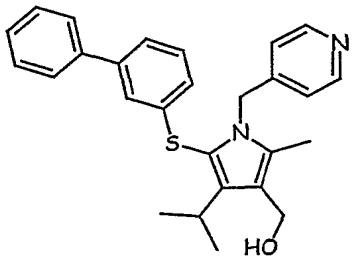
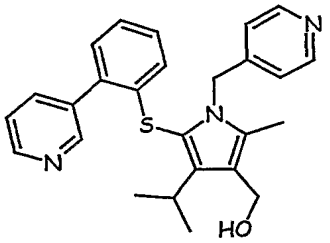
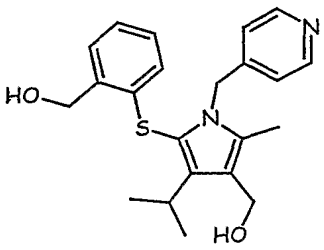
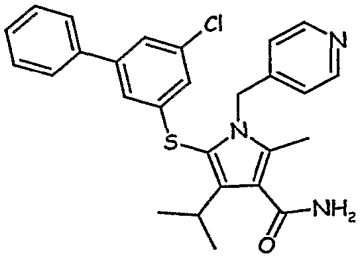
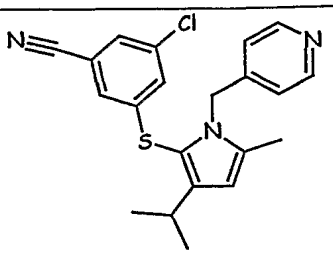
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol
	[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl acetate
	5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carbaldehyde
	4-[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-pyrrol-2-yl]-but-3-en-2-one
	4-[[2-(3,5-Dichlorophenylthio)-5-methyl-3-phenyl-1-pyrrolyl]methyl]pyridine
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine

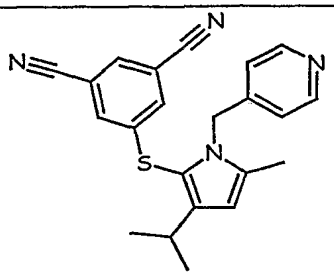
	5-(3,5-Dichlorophenylthio)-N-(2,4,6-trimethoxybenzyl)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid trifluoroacetate (1:1)
	5-(3,5-Dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carbonitrile
	5-(3,5-Dichlorophenylthio)-4-isopropyl-N,2-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide

	5-(3,5-Dichlorophenylthio)-4-cyclopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxanilide
	5-(3,5-Dichlorophenylthio)-4-isopropyl-N,N,2-trimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3-Allyl-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-(3-Chloro-5-propylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide

	5-(3-Chloro-5-vinylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-[3-Chloro-5-(2(RS),3-dihydroxypropyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	4-[[2-(3,5-Dichlorophenylthio)-5-(ethoxymethyl)-3-isopropyl-1-pyrrolyl]methyl]pyridine
	4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-(methoxymethyl)-1-pyrrolyl]methyl]pyridine
	[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl carbamate

	4-[[2-(3-Bromo-5-chlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine
	4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridine
	4-[[2-(3-Chloro-5-propylphenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine
	5-(3-Chloro-5-ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	5-[3-Chloro-5-(hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide

	5-(2-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-methanol
	5-(3-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	4-Isopropyl-2-methyl-1-[(4-pyridyl)methyl]-5-[2-(3-pyridyl)phenylthio]-1H-pyrrole-3-methanol
	5-[2-(Hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol
	5-(5-Chloro-3-biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide
	3-Chloro-5-[3-isopropyl-5-methyl-1-[(4-pyridinyl)methyl]-1H-pyrrol-2-ylthio]benzonitrile

	5-[3-Isopropyl-5-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-ylthio]-1,3-dibenzonitrile

The compounds of formula I and hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof are inhibitors of the human immunodeficiency virus reverse transcriptase enzyme both in vitro and in vivo, and can be used in the control or prevention of diseases mediated by the human immunodeficiency virus (HIV).

The pyrrole derivatives provided by the present invention are useful in therapeutic treatment of the human or animal body.

The pyrrole derivatives provided by the present invention are inhibitors of the human immunodeficiency virus reverse transcriptase enzyme. Accordingly, the present pyrrole derivatives are therapeutically active substances in the treatment of diseases mediated by the human immunodeficiency virus (HIV) and can be used as medicaments for the treatment of such diseases.

They can be used as medicaments, especially for treating viral diseases, immune mediated conditions or diseases, bacterial diseases, parasitic diseases, inflammatory diseases, hyperproliferative vascular diseases, tumors, and cancer.

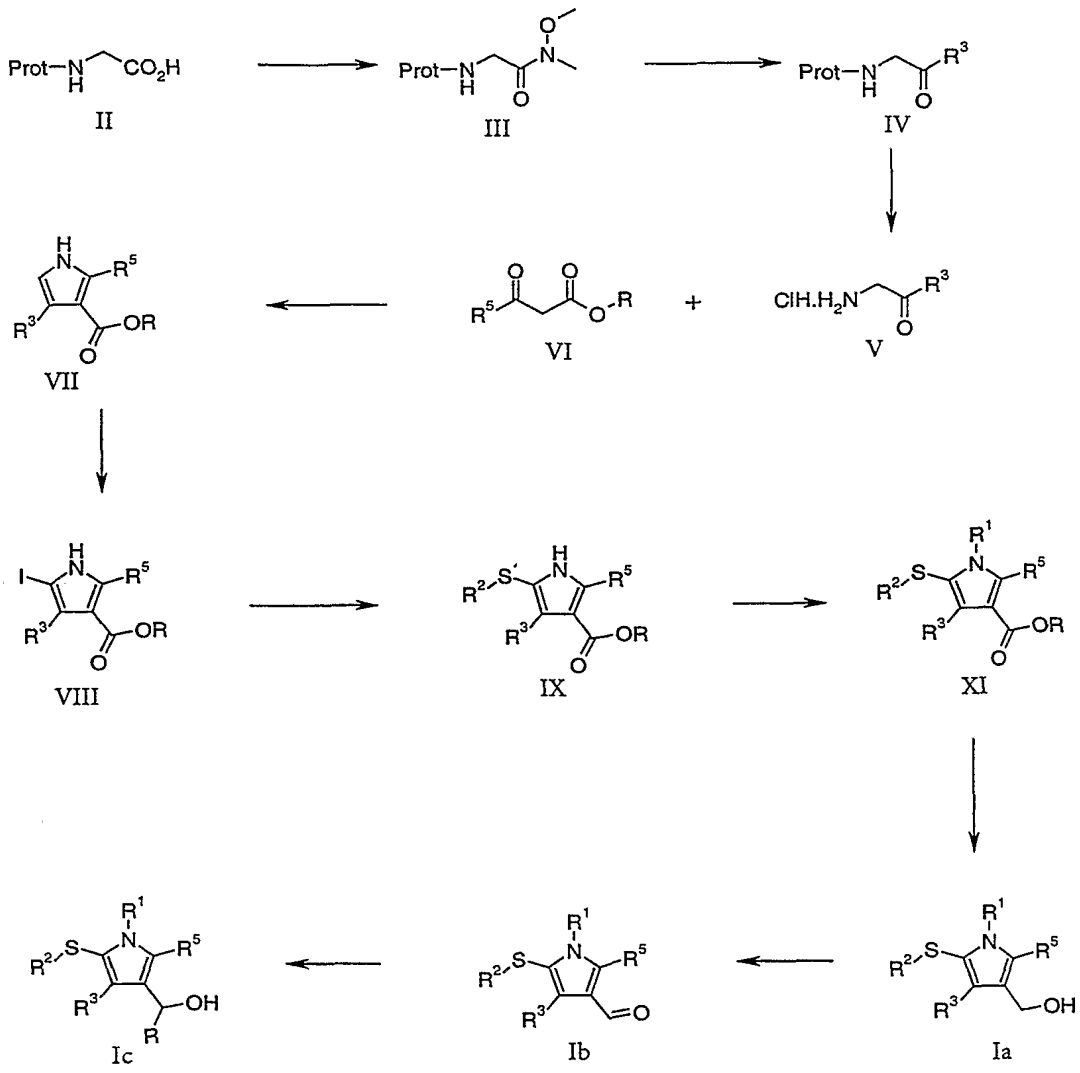
In particular, compounds of the present invention and pharmaceutical compositions containing the same are useful as chemotherapeutic agents, inhibitors of viral replication and modulators of the immune system, and can be used for the treatment of diseases mediated by the human immunodeficiency virus (HIV) other viral diseases such as retroviral infections (either alone or in combination with other antiviral agents such as interferon or derivatives thereof, such as conjugates with polyethylene glycol).

They can be used alone, or in combination with other therapeutically active agents, for example, an immunosuppressant, a chemotherapeutic agent, an anti-viral agent, an antibiotic, an anti-parasitic agent, an anti-inflammatory agent, an anti-fungal agent and/or an anti-vascular hyperproliferation agent.

Compounds, whenever prepared by the processes of the present invention are also an object of the present invention.

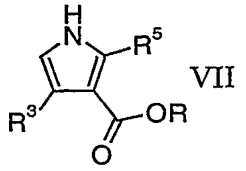
The compounds of the present invention can be prepared as shown in the following scheme.

Reaction scheme 1:



wherein R^1, R^2, R^3, R^5 and R are as defined for compounds of formula I and and Prot is an amino protecting group.

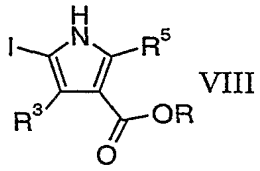
In accordance with the present invention, compounds of formula VIII are prepared by reacting the compound of formula VII



VII

wherein R, R^3 and R^5 are as described in formula I

with a iodination agent to obtain the iodo pyrrole derivative of formula VIII



VIII

wherein R, R^3 and R^5 are as described in formula I.

The iodination agent used for this reaction are known in the art and are for example N-iodosuccinimide, iodic acid in the presence of iodine, iodine in the presence of potassium iodide or sodium iodide, potassium iodide or sodium iodide in the presence of hydrogen peroxide.

The reactions can be carried out in a conventional manner known to the skilled in the art.

In Reaction scheme I, N-protected glycine (commercially available from Fluka) of formula II is reacted with N,O-dimethylhydroxylamine hydrochloride in the presence of N-ethylmorpholine and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride under nitrogen atmosphere. The term "amino protecting group" (Prot) as used herein refers to groups such as those employed in peptide chemistry such as a tert.-butoxycarbonyl group (t-BOC) or a benzyloxycarbonyl group (Z). Preferred amino protecting group (Prot) for this reaction is a tert.-butoxycarbonyl group. The reaction is conveniently carried out at a reaction temperature from 0°C to room temperature in an inert solvent, for example halogenated hydrocarbons such as anhydrous dichloromethane or polar aprotic solvents such as N,N-dimethylformamide (DMF) or tetrahydrofuran (THF) preferably dichloromethane, to yield the N-protected glycine N-methyl-N-methoxyamide of formula III.

The N-protected glycine N-methyl-N-methoxyamide of formula III is converted to the compound of formula IV by reaction with a Grignard reagent of the formula R^3MgX (commercially available or synthesized according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions,

Mechanisms, and Structure", 4th ed. John Wiley & Sons) wherein R^3 is as defined above but not hydrogen (for R^3 being hydrogen, the reaction sequence starts with compound of the formula V; see below) and X represents a halogen for example chlorine. The reaction is conveniently carried out in an inert solvent, for example ethers such as anhydrous tetrahydrofuran, diethyl ether, dioxane or a mixture of the mentioned solvents at a reaction temperature from 0°C to room temperature. After the reaction, the Grignard product is worked-up in a manner known in the art for example with a solution of diluted hydrochloric acid, to yield the N-protected α-amino ketone of formula IV.

In the next step of the reaction, the N-protected α-amino ketone of formula IV is reacted with trifluoroacetic acid or with hydrogen chloride thereby obtaining the deprotected α-amino ketone of formula V. In forming the compound of formula V, any conventional method for deprotection reactions of protected amino groups can be utilized in carrying out this reaction. The deprotection reaction of the compounds of formula IV is preferably carried out with trifluoroacetic acid optionally dissolved in dichloromethane or hydrogen chloride dissolved in ethyl acetate, dioxane or methanol at a reaction temperature from 0°C to room temperature. Most preferred, the deprotection reaction is carried out with hydrogen chloride dissolved in ethyl acetate.

The α-amino ketone of formula V is coupled with a β-keto ester of the formula VI wherein R^5 and R are as defined above (commercially available or synthesized according to methods known from textbooks on heterocyclic chemistry or organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to form a pyrrole derivative of the formula VII. The synthesis of the pyrrole derivatives according to the Knorr synthesis of the formula VII is carried out in a manner known in the art. The reaction of the compounds of formula V and VI to yield compounds of the formula VII is preferably carried out with a mixture of potassium hydroxide and K_2HPO_4 in water at a reaction temperature from 20 to 40°C. Most preferred, the reaction is carried out with a mixture of ethyl acetoacetate, sodium acetate and acetic acid at a reaction temperature from 70 to 100°C.

In the next step of the reaction, an iodo pyrrole derivative of formula VIII is formed by the reaction of pyrrole derivative of the formula VII with an iodination agent. The iodination agent used for this reaction is known in the art and are for example N-iodosuccinimide, iodic acid in the presence of iodine, iodine in the presence of potassium iodide or sodium iodide, potassium iodide or sodium iodide in the presence of hydrogen peroxide. The reaction is for example carried out in an inert solvent, such as ethers, hydrocarbons or halogenated hydrocarbons preferably anhydrous dichloromethane at a reaction temperature from 0 to 40°C, preferably at room temperature in the presence of a iodination agent for example N-iodosuccinimide to yield the iodo pyrrole derivative of

formula VIII. After the reaction, the product is worked-up in a manner known in the art for example the mixture is washed with an aqueous solution of sodium thiosulphate and an aqueous solution of sodium hydrogen carbonate, dried over anhydrous sodium sulphate and finally the organic solvent was evaporated. The reaction is known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons or as described in Y. Murata, Bull. Chem. Soc. Jpn. 1996 (11), 3339. The use of above-mentioned iodination agents is described for example in Synthesis 1995 (12), 1480, Tetrahedron 1992 (48) 44, 9661 or Liebigs Ann. Chem. 1989 (9), 863.

The iodo pyrrole derivatives of formula VIII are converted to the corresponding pyrrole thio compounds of formula IX by reaction with a disulphide compound of the formula R^2SSR^2 or by the reaction with a compound of the formula R^2SX wherein R^2 is as defined above and X is a halogen, preferably chlorine (the compounds of the formula R^2SSR^2 and R^2SX are commercially available or can be synthesized according to methods known from the art for example as described in US 4,282,242). The reaction is conveniently carried out by treating the compound of formula VIII under nitrogen atmosphere with a strong base for example sodium hydride or preferably lithium hydride, in an inert solvent for example anhydrous dimethyl sulphoxide at a reaction temperature from 0°C to room temperature and then reacting the mixture with the compounds of the formula R^2SX or preferably with the disulphide compound of the formula R^2SSR^2. The reaction is preferably carried out at a reaction temperature from 40 to 60°C, yielding the compound of formula IX. After the reaction, the product is worked-up in a manner known in the art for example extracted with diethyl ether, dried over anhydrous magnesium sulphate and finally the organic solvent is evaporated.

In the next step of the reaction, the compound of formula IX is reacted with a compound of the formula R^1X wherein R^1 is as defined above but not hydrogen (the compound for R^1 being hydrogen has already been described; see compound IX) and X represents a halogen for example bromo (commercially available or synthesized according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to obtain the N-substituted compound of the formula XI. In forming the compound of formula XI, any conventional method of substitution can be utilized in carrying out this reaction. The reaction of the compounds of formulas IX is preferably carried out under nitrogen in an inert solvent for example polar aprotic solvents such as tetrahydrofuran (THF) or N,N-dimethylformamide (DMF), preferably anhydrous THF at a temperature from 0°C to room temperature in the presence of tetra-n-butylammonium bromide and in the presence of a base such as sodium hydroxide, potassium carbonate,

sodium hydride or an amine of the formula R_3N wherein R is methyl, ethyl or propyl. Most preferred base is sodium hydroxide. Finally the mixture is reacted with the compound of the formula R^1X to obtain the compound of formula XI.

The conversion of a compound of the formula XI to a compound of the formula Ia wherein R, R^1, R^2, R^3 and $R^5$are as defined above and R^4 is CH_2OH and X represents S, is carried in that the compound of formula XI is reduced to the compound of formula Ia by reacting it with a reducing agent such as lithium aluminium hydride. The reaction is conveniently carried out by treating the compound of formula XI under nitrogen atmosphere with a reducing agent for example $LiAlH_4$, $LiBH_4$, $BH_3{}^*S(CH_3)_2$, iso-Bu_2AlH or Vitride®, in an inert solvent such as ethers for example anhydrous diethyl ether, THF of dioxane at a reaction temperature from 0°C to room temperature. Preferably, the reaction is carried out with $LiAlH_4$ and ethers. Then a solution of ammonium chloride is added to yield to a compound of the formula Ia. After the reaction, the product is worked-up in a manner known in the art for example extracted with ethyl acetate, dried over anhydrous magnesium sulphate and finally the organic solvent is evaporated.

Oxidation of a compound of the formula Ia to a compound of the formula Ib wherein R, R^1, R^2, R^3 and $R^5$are as defined above, R^4 is C(=O)H and X represents S, is carried in that the compound of formula Ia is oxidized with an oxidizing reagent such iodobenzene diacetate in the presence of 2,2,6,6-tetramethylpiperidine N-oxide, $(COCl)_2$ in the presence of dimethyl sulfoxide (DMSO), pyridinium chlorochromate in dichloromethane or MnO_2 in ethers such as diethyl ether or in a halogenated hydrocarbons such as anhydrous dichloromethane or trichloromethane or in an aprotic polar solvent such as acetone and a compound of the formula Ib is obtained. The reaction is conveniently carried out by treating the compound of formula Ia under nitrogen atmosphere with an oxidizing agent, preferably iodobenzene diacetate and 2,2,6,6-tetramethylpiperidine N-oxide, in an inert solvent for example anhydrous dichloromethane at a reaction temperature from 0°C to room temperature to yield to a compound of the formula Ib. After the reaction, the product is worked-up in a manner known in the art for example washed with solutions of sodium thiosulphate and sodium hydrogen carbonate dried over anhydrous sodium sulphate and finally the organic solvent is evaporated.

Conversion of a compound of the formula Ib to a compound of the formula Ic wherein R, R^1, R^2, R^3 and $R^5$are as defined above and R^4 is CH(R)OH and X represents S, is carried in that the compound of formula Ib is reacted with a Grignard reagent of the formula RMgX or a reagent of the formula RLi (both compounds are commercially available or can be synthesized according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions,

Mechanisms, and Structure", 4th ed. John Wiley & Sons) wherein R is as defined above but not hydrogen (for R being hydrogen, the synthesis has already been described; see compound of the formula Ia) and X represents a halogen for example bromo to yield to a compound of the formula Ic. The reaction is conveniently carried out by treating the compound of formula Ib under nitrogen atmosphere, in an inert solvent for example ethers such as anhydrous tetrahydrofuran (THF), diethyl ether or dioxane, preferably THF with a Grignard reagent of the formula RMgX, preferably methyl magnesium bromide at a reaction temperature from 0°C to room temperature and then a solution of ammonium chloride is added to yield to a compound of the formula Ib. After the reaction, the product is worked-up in a manner known in the art for example extracted with ethyl acetate dried over anhydrous magnesium sulphate and finally the organic solvent is evaporated.

Compounds of the formula Ia wherein R, R^1, R^2, R^3 and $R^5$are as defined above, R^4 is hydrogen and X represents S, are synthesized according to known methods from the art. For example the ester compounds of the formula XI are hydrolysed to the corresponding carboxylic acid according to methods known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons. In a second step carboxylic acid function of the pyrrole derivative is then decarboxylated according to methods known in the art and for example described in S. F. Macdonald, J. Chem. Soc. 1952, 4176 or G. Kleinspehn, J. Am. Chem. Soc. 1954, 76, 5641.

Compounds of the formula Ia wherein R, R^1, R^2, R^3 and $R^5$are as defined above, R^4 is alkyl and X represents S, are synthesized according to known methods from the art. For example the compounds can be synthesised through elimination reaction of a compound of the formula Ic in a two step reaction, first in the presence of CH_3SO_2Cl and Et_3N and secondly with a base such as potassium hydroxide or sodium hydroxide to form the corresponding alkenyl compound which is subsequently hydrogenated in the presence of hydrogen and palladium on activated coal (Pd/C) to the corresponding alkyl substituted pyrrole derivative. The reaction are all known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons.

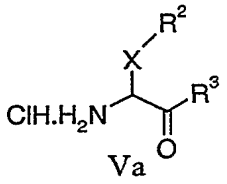
Compound of the formula I wherein R, R^1, R^2, R^3 and $R^5$are as defined above and R^4 is C(=O)R wherein R is alkyl are synthesized according to known methods from the art. For example, the hydroxy compounds of the formula Ic are oxidised according to methods known from the art for example from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to obtain the corresponding oxo derivatives.

Compounds of the formula I wherein R, R^1, R^2, R^3 and $R^5$are as defined above and R^4 is $CONR_2$ are synthesized according to known methods from the art. For example, the ester compounds of the formula XI is hydrolysed as described above, then reacted with thionyl chloride to obtain the activated acid chloride and finally reacted with a compound of the formula HNR_2 wherein R is hydrogen or alkyl to obtain the corresponding amide derivative. The reaction are all known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons.

Compounds of the formula I wherein R, R^1, R^2, R^3 R^4 and $R^5$are as defined above and X is S(O) or S(O)2 are synthesized according to known methods from the art. For example, the compounds of the formula I, Ia, Ib or Ic are oxidized, to obtain the corresponding oxidised thio compounds derivatives. The reaction is known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons.

Compounds of the formula I wherein R, R^1, R^2, R^3 R^4 and $R^5$are as defined above and X is O or N(alkyl) are synthesized according to known methods from the art. For example, the compounds of the formula VII are reacted with N-bromosuccinimide (NBS) to obtain the corresponding 2-substituted bromopyrrole which is further reacted with a neutral oxygen nucleophile, such as 3-methoxyphenol in the presence of Et_3N to obtain the corresponding oxy pyrrole derivative. To obtain the corresponding N-substituted pyrrole derivatives, the above-mentioned 2-substituted bromopyrrole is reacted with a secondary amine in a polar aprotic solvent such as N,N-dimethylformamide (DMF). The reactions are all known in the literature for example from textbooks on organic chemistry e.g. J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons or G. Cirrincione et al., Synthesis, 1997, 1169.

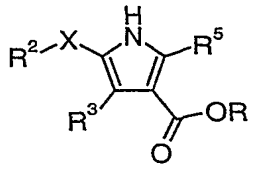
Compounds of the formula I wherein R, R^1, R^2, R^3 R^4 and $R^5$are as defined above and X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl are synthesized according to known methods from the art. For example, compounds of the formula Va



Va

wherein R^3 is as defined above and X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl are coupled with a β-keto ester of the formula VI wherein R^5 and R are as defined above

(commercially available or synthesized according to methods known from textbooks on heterocyclic chemistry or organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons) to form a pyrrole derivative of the formula VIIa

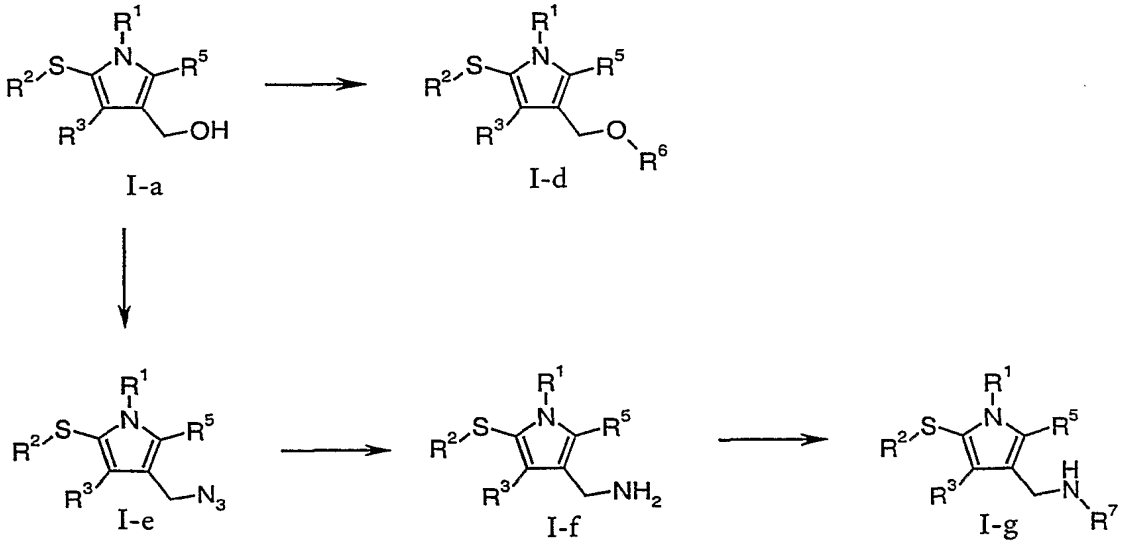


VIIa

wherein R, R^3, R^5 and X-R^2 are as defined above. The synthesis of the pyrrole derivatives according to the Knorr synthesis of the formula VIIa is carried out in a manner known in the art. Subsequently the compound of the formula VIIa is further reacted according the above-described reactions starting with compound IX→XI→Ia→Ib→Ic.

The compounds of formula VIII are new intermediates and therefore also subject of the present invention.

Reaction scheme 2:



wherein R^1, R^2, R^3, and R^5 are as defined for compounds of formula I, R^6 is C_{1-4}-alkyl and R^7 taken together with the amino-methyl group is 2-pyridyl-carbonyl-amino-methyl, 3-pyridyl-carbonyl-amino-methyl, 4-pyridyl-carbonyl-amino-methyl, (amino-methyl)-

carbonyl-amino-methyl, (phenoxy)-carbonyl-amino-methyl, (methoxy)-carbonyl-amino-methyl, (di-methyl-amino)-carbonyl-amino-methyl, (phenyl-amino)-carbonyl-amino-methyl, (amino)-carbonyl-amino-methyl, (phenyl)-carbonyl-amino-methyl, (methyl)-carbonyl-amino-methyl, methyl-carbonyl-amino-methyl-carbonyl-amino-methyl, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino-methyl, (N1-Acetyl-O-tert.-butyl-N2-ylmethyl)-L-serinamide, (N1-Acetyl-N2-yl]methyl)-L-serinamide, [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl-methyl]-L-serinamide, methyl-sulfonyl-amino-methyl, phenyl-sulfonyl-amino-methyl or p-toluyl-sulfonyl-amino-methyl.

The primary alcohol I-a may be alkylated, acylated or reacted with isocyanates to give carbamates according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons. These are standard reactions of which there are many combinations of reagents, for example, alkylation may be achieved using alkyl iodides, bromides, chlorides, triflates or any other suitable leaving group. Acylation may be achieved via acid chlorides or other activated carbonyl compounds such as activated carboxylic acids. Carbamates are accessible by reacting I-a with isocyanates in a standard procedure.

I-a may be further derivatised to the azide I-e using sodium azide or diphenylphosphoryl azide in standard procedures according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons. . I-e may be reduced to the primary amine I-f using hydrogenation with standard catalysts such as 10% palladium on carbon in suitable solvents, such as ethyl acetate, methanol or ethanol, or with a trialkyl or aryl phosphine.

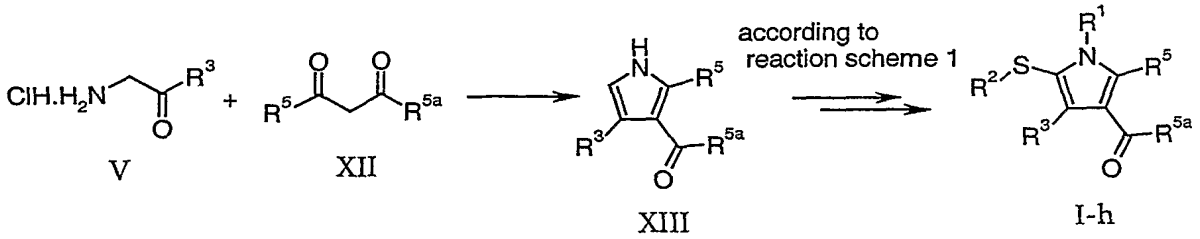
The primary amine I-f may be alkylated, acylated, sulfonylated or reacted with isocyanates (to give ureas) to give I-g according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons. These are standard reactions of which there are many combinations of reagents, for example, alkylation may be achieved using alkyl iodides, bromides, chlorides, triflates or any other suitable leaving group. Acylation may be achieved via acid chlorides or other activated carbonyl compounds such as activated carboxylic acids. Sulfonylation may be via sulfonyl chlorides using a base such as triethylamine, N-methyl morpholine or N-ethyl morpholine. All these reactions may be

conducted in suitable solvents known to those skilled in the art, for example, dichloromethane, chloroform, dioxane, dimethyformamide, tetrahydrofuran, etc.

Ureas are accessible by reacting I-f with isocyanates in a standard procedure.

Derivatives of ester XI (reaction scheme 1), where the ester is replaced by other carbonyl groups (see reaction scheme 3), may be prepared according to reaction scheme 1 where the only change is intermediate VI for intermediate XII:

Reaction scheme 3 (additional reagents of type VI):

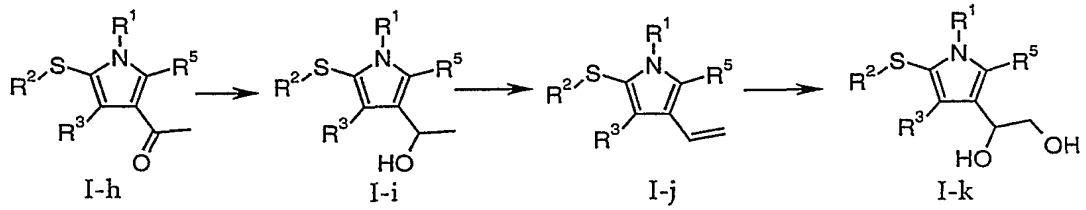


wherein R^1, R^2 and $R^{3,}$ are as defined for compounds of formula I, where R^5 is alkyl and R^{5a} is hydrogen, amino, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl.

The chemistry to form the pyrrole and the subsequent reactions are as for those reactions already described in reaction scheme 1.

When R^{5a} = methyl, yet further derivatives of the pyrrole may be prepared according to reaction scheme 4:

Reaction scheme 4:

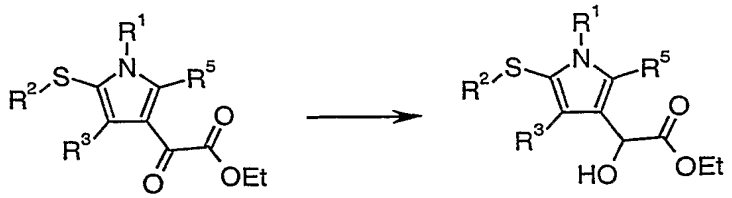


wherein R^1, R^2, R^3, and R^5 are as defined for compounds of formula I.

I-h, prepared according to reaction scheme 3, may be reduced to the ethanol derivative I-i as already described. Elimination of water to form the vinyl compound I-j is achieved thermally by heating in a high boiling solvent such as DMSO, DMF, N-methyl pyrrolidinone, etc. Conversion of I-j into diol I-k may be achieved with osmium tetroxide, a standard reaction according to methods known from textbooks on organic chemistry e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons.

Ketone reduction of I-l (when R^{5a} = COCOOEt) to form I-m is achieved using the same chemistry as for preparation of I-i:

Reaction scheme 5:

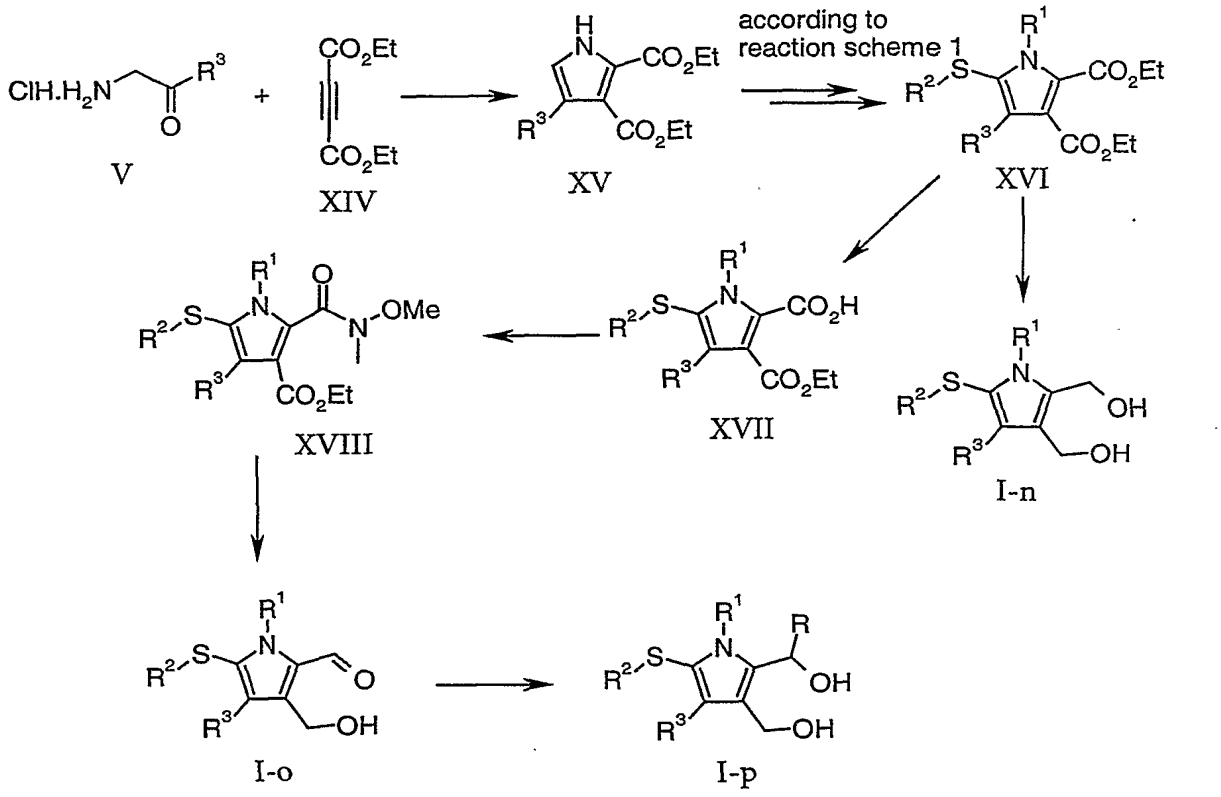


made via intermediate XII
(reaction scheme 3)
according to reaction scheme 1

wherein R^1, R^2, R^3, and R^5 are as defined for compounds of formula I.

The pyrrole may also be constructed using a cycloaddition reaction according to the method of Yavari, Synthetic Communications, 1996, 4495-4500 (reaction scheme 6).

Reaction scheme 6:



wherein R^1, R^2 and R^3, are as defined for compounds of formula I.

In reaction scheme 6, the amino ketone V is reacted with diethylacetylene dicarboxylate of formula XIV in sodium acetate in refluxing ethanol to give an intermediate which is cyclised with acid giving XV. Other acetylenic esters may be used such as methyl, benzyl or aryl in a range of alcoholic solvents such as propanol or butanol.

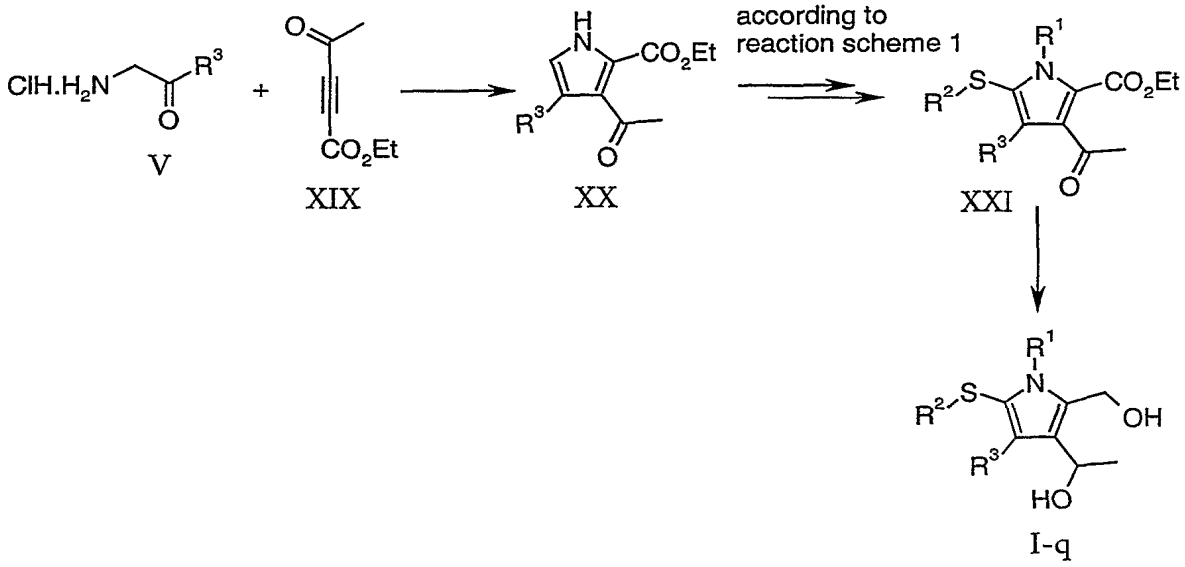
Intermediate XV may be converted to XVI according to methods already described in reaction scheme 1.

Reduction of both esters in XVI to give I-n may be accomplished according to the preparation of 1a from X1 (see Reaction Scheme 1), preferably with lithium aluminium hydride in ether.

Using basic hydrolysis, the 2-position ester may be selectively cleaved to give carboxylic acid XVII. Any strong mineral base is suitable for this purpose, preferably hydroxide ions (sodium or potassium hydroxide), in an alcoholic solvent such as ethanol, propanol, butanol.

XVII may then be derivatised with N,O-dimethyl hydroxylamine according to intermediate III (see Reaction Scheme 1) to give the amide XVIII. Reduction of this amide and the ester in XVIII with lithium aluminium hydride (as above for the synthesis of I-n) gives aldehyde I-o. Grignard addition to the aldehyde in I-o gives compounds I-p, using the same method as for the synthesis of I-c (reaction scheme 1).

Reaction scheme 7:

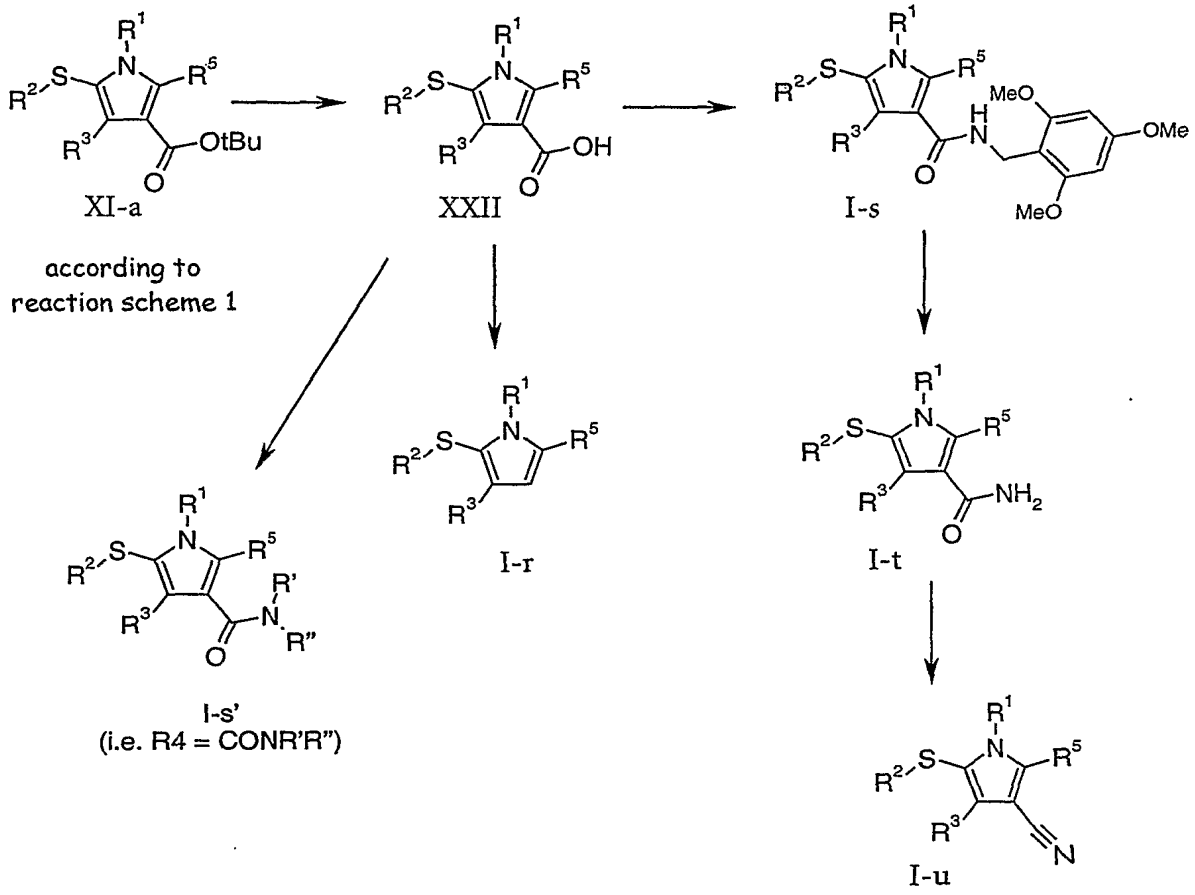


wherein R^1, R^2 and R^3, are as defined for compounds of formula I.

Preparation of intermediate XX may be constructed using a cycloaddition reaction according to the method of Yavari, Synthetic Communications, 1996, 4495-4500 (Scheme 2a), as for intermediate XV.

Reduction of the ester and ketone in XXI to give I-q may be accomplished with lithium aluminium hydride in ether, as for I-p and I-a.

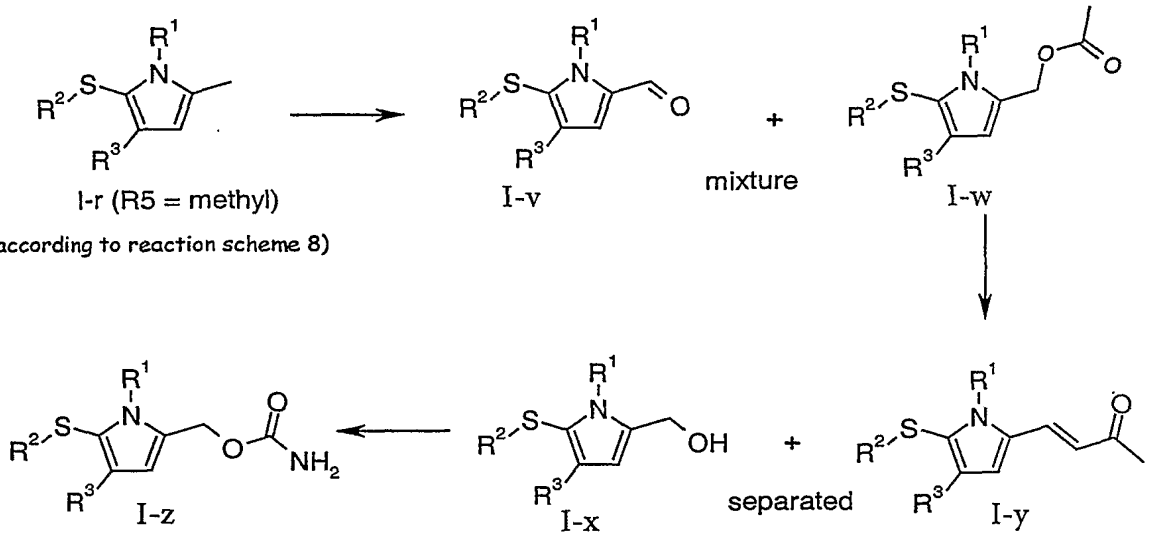
Reaction scheme 8:



wherein R^1, R^2, R^3, and R^5 are as defined for compounds of formula I.

Tert.-butyl ester XI-a (prepared according to reaction scheme 1) may be hydrolysed using methods known in the art, such as trifluoroacetic acid in dichloromethane, to give the carboxylic acid XXII, a versatile intermediate which may be either thermally decarboxylated to I-r or derivatised further to amide I-s. Similar amide bond formations of XXII may be carried out with a variety of amines to give amides I-s' where, R' and R" are defined above. Treatment of I-s with trifluoroacetic acid in dichloromethane reveals the primary amide I-t. Dehydration of I-t to give I-u may be achieved with Lawessons reagent according to Cava, Michael P.; Levinson, Matthew I Tetrahedron (1985), 41(22), 5061-87, which gives the nitrile

Reaction scheme 9:

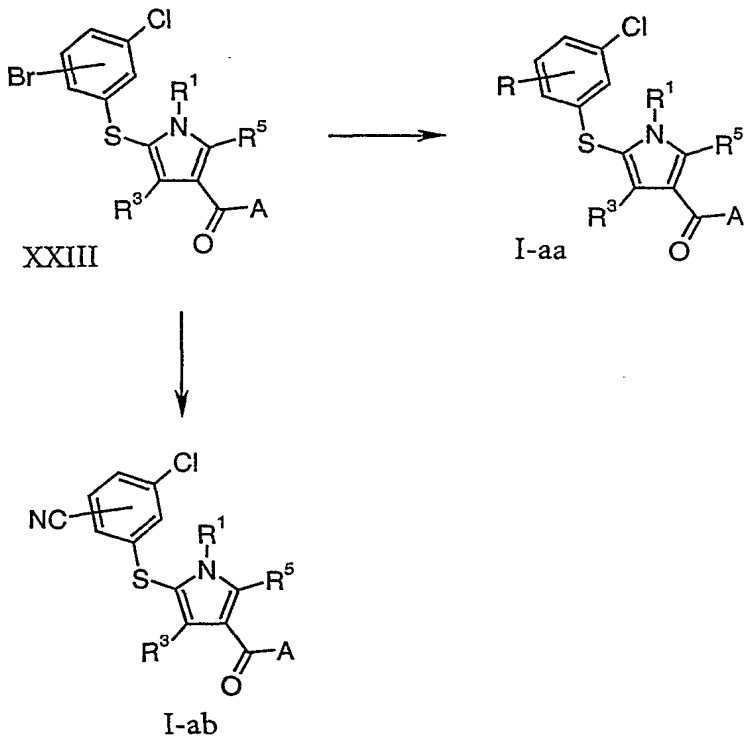


wherein R^1, R^2 and R^3, are as defined for compounds of formula I.

In reaction scheme 9, compound I-r (R^5 = methyl, synthesized according to reaction scheme 8), may be oxidised with lead tetraacetate to give a mixture of the aldehyde I-v and acetate I-w. Lead tetraacetate is a well known oxidant to those skilled in the art but other oxidants, such as potassium permanganate may also be used to oxidise aromatic methyl groups as in I-r.

Acetate I-w (crude) may then be hydrolysed to primary alcohol I-x using any method known in the art, such as alkaline hydrolysis with sodium or potassium hydroxide. On purification the by-product I-y was isolated. Alcohol I-x may then be derivatised to the primary carbamate I-z using trichloroacetyl isocyanate. The starting alcohol may be conveniently dissolved in a suitable organic solvent such as dichloromethane or chloroform and the reagent trichloroacetyl isocyanate added keeping the reaction temperature below 5 degrees but above –10 degrees. The work up involves use of bases such as sodium or potassium carbonate followed by purification using standard procedures. Other methods known in the art are not effective in this transformation, such as chlorosulfonyl isocyanate or trimethylsilyl isocyanate.

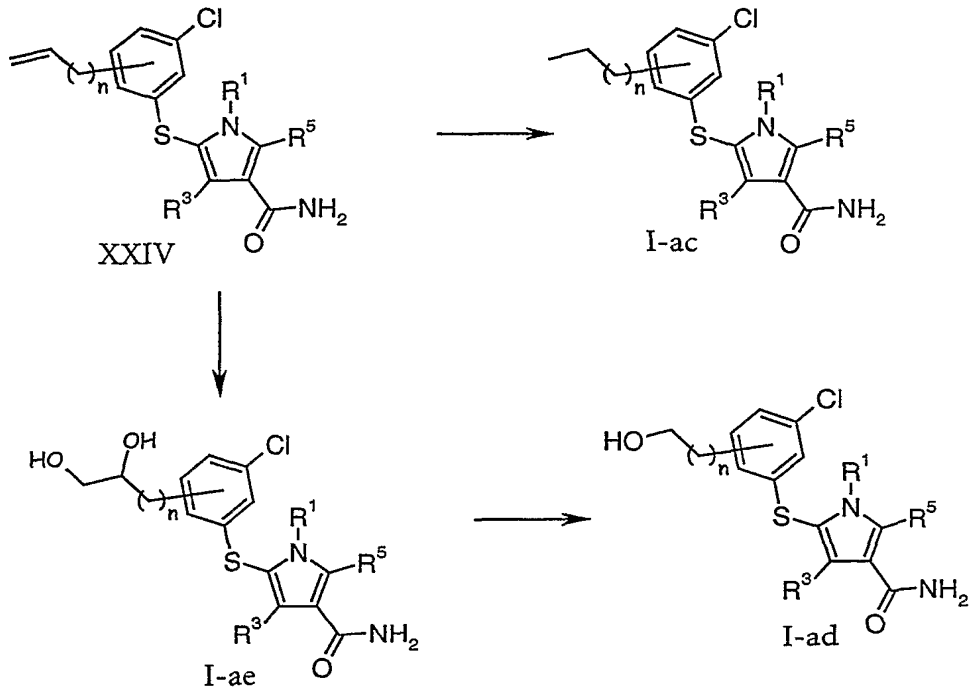
Reaction scheme 10:



wherein R^1, R^3 and R^5 are as defined for compounds of formula I, A is C1-4-alkoxy or amino and R is C_{1-4}-alkyl.

In reaction scheme 10, intermediate XXIII (synthesized according to reaction scheme 1 using 3-bromo-5-chlorophenyldisulfide) may be transformed to I-aa using sp2-sp2 coupling reactions known to persons skilled in the art (e.g. from J. March (1992), "Advanced Organic Chemistry : Reactions, Mechanisms, and Structure", 4th ed. John Wiley & Sons). Such reactions are typically catalysed by a suitable palladium species such as tetrakis(triphenylphosphine) palladium, palladium acetate or dibenylideneacetone palladium. Nitrile groups may be installed using the reactivity of the aryl bromide XXIII using copper (I) cyanide to give I-ab. This reaction may also be performed on the aryl dibromide to give the aryl dinitrile.

Reaction scheme 11:



wherein R^1, R^3 and R^5 are as defined for compounds of formula I and n is 0 or 1.

In reaction scheme 11, intermediate XXIV, a subset of XXIII, may be reduced to the saturated alkyl chain I-ac by palladium catalysed hydrogenation. Oxidation of XXIV via osmium catalysed dihydroxylation gives I-ae. Sodium periodate cleavage of I-ae gives alcohol I-ad, according to standard procedures well known in the art.

The following assay methods are described.

HIV-1 reverse transcriptase assay: Inhibitor IC_{50} determination.

HIV-1 RT assay was carried out in 96-well Millipore filtermat NOB50 plates using purified recombinant enzyme and a poly(rA)/oligo$(dT)_{16}$ template-primer in a total volume of 50 µL. The assay constituents were 50 mM Tris/HCl, 50 mM NaCl, 1 mM EDTA, 6 mM $MgCl_2$, 5 µM dTTP, 0.1 µCi [^{3}H] dTTP, 5 µg/ml poly (rA) pre annealed to 2.5 µg/ml oligo $(dT)_{16}$ and a range of inhibitor concentrations in a final concentration of 10% DMSO. Reactions were initiated by adding 5 nM HIV-1 RT and after incubation at 37^{0}C for 30 min, they were stopped by the addition of 50 µl ice cold 20%TCA and allowed to precipitate at 4^{0}C for 30 min. The precipitates were collected by applying vacuum to the plate and sequentially washing with 2 x 200 µl of 10% TCA and 2 x 200 µl 70% ethanol. Finally the plates were dried and radioactivity counted in a Wallac Microbeta 1450 after the addition of 15 µl scintillation fluid per well. $IC_{50's}$ were calculated by plotting % inhibition versus $\log_{10}$ inhibitor concentrations.

Antiviral assay method

Anti-HIV antiviral activity was assessed using an adaptation of the method of Pauwels et al. {Pauwels et al., 1988, J Virol Methods 20:309-321}. The method is based on the ability of compounds to protect HIV-infected T lymphoblastoid cells (MT4 cells) from cell-death mediated by the infection. The endpoint of the assay was calculated as the concentration of compound at which the cell viability of the culture was preserved by 50% ('50% inhibitory concentration', IC_{50}). The cell viability of a culture was determined by the uptake of soluble, yellow 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) and its reduction to a purple insoluble formazan salt. After solubilization, spectrophotometric methods were employed to measure the amount of formazan product.

MT4 cells were prepared to be in logarithmic-phase growth and a total of 2 x 10^6 cells infected with the HXB2-strain of HIV at a multiplicity of 0.0001 infectious units of virus per cell in a total volume of between 200-500 microlitres. The cells were incubated with virus for one h at 37°C before removal of virus. The cells are then washed in 0.01 M phosphate buffered saline, pH 7.2 before being resuspensed in culture medium for incubation in culture with serial dilutions of test compound. The culture medium used was RPMI 1640 without phenol red, supplemented with penicillin, streptomycin, L-glutamine and 10% fetal calf serum (GM10).

Test compounds were prepared as 2 mM solutions in dimethyl sulphoxide (DMSO). Four replicate, serial 2-fold dilutions in GM10 were then prepared and 50 microlitres amounts placed in 96-well plates over a final nanomolar concentration range of 625 – 1.22.

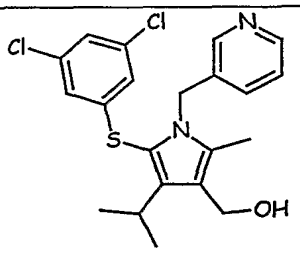
Fifty microlitres GM10 and 3.5 x 10^4 infected cells were then added to each well. Control cultures containing no cells (blank), uninfected cells (100% viability; 4 replicates) and infected cells without compound (total virus-mediated cell death; 4 replicates) were also prepared. The cultures were then incubated at 37 °C in a humidified atmosphere of 5% CO_2 in air for 5 d.

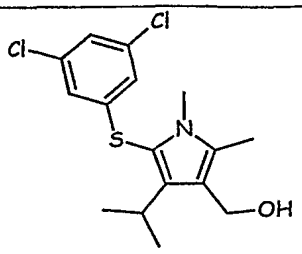
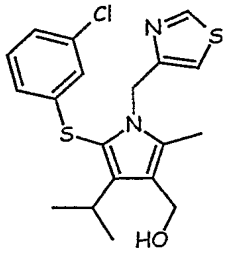
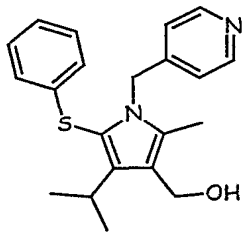
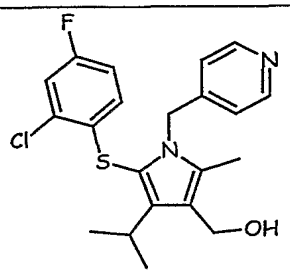
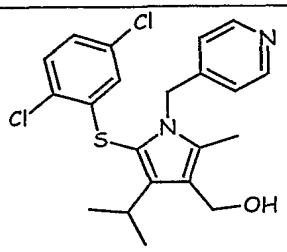
A fresh solution of 5 mg/mL MTT was prepared in 0.01 M phosphate buffered saline, pH 7.2 and 20 microlitres added to each culture. The cultures were further incubated as before for 2 h. They were then mixed by pipetting up and down and 170 microlitres of Triton X-100 in acidified isopropanol (10% v/v Triton X-100 in 1:250 mixture of concentrated HCl in isopropanol). When the formazan deposit was fully solubilized by further mixing, the absorbance (OD) of the cultures was measured at 540nm and 690nm wavelength (690nm readings were used as blanks for artefacts between wells). The percent protection for each treated culture can be calculated from the equation:

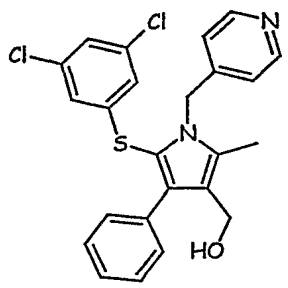
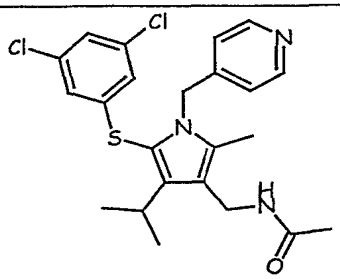
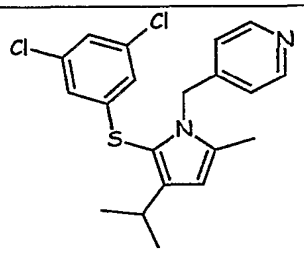
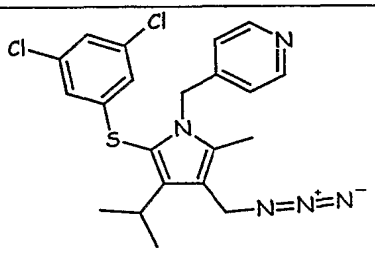
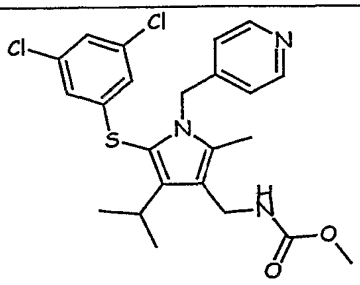
% Protection =

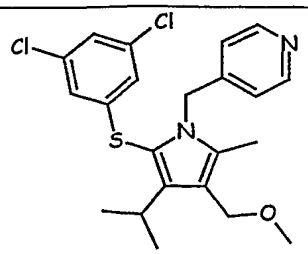
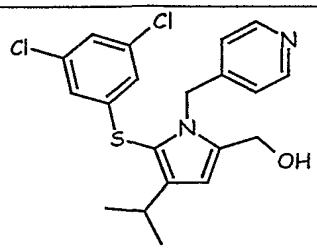
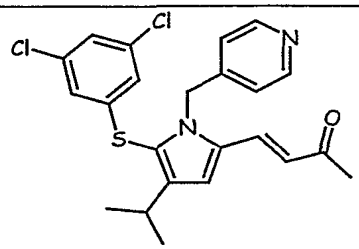
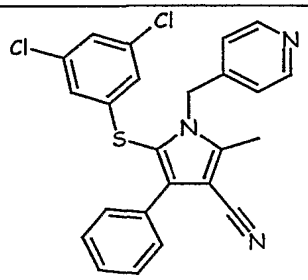
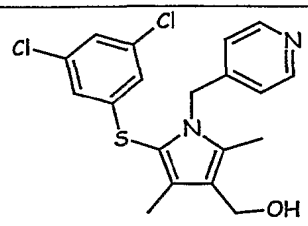
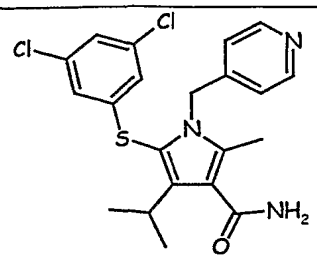
$$\frac{\text{(OD drug-treated cultures)} - \text{(OD untreated virus control cultures)}}{\text{(OD uninfected cultures)} - \text{(OD untreated virus control cultures)}} \times 100\%$$

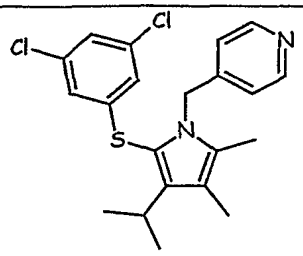
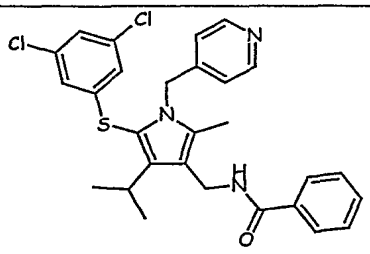
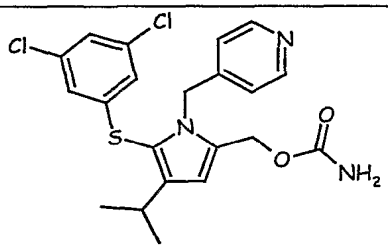
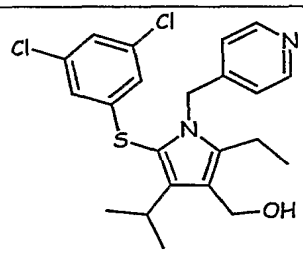
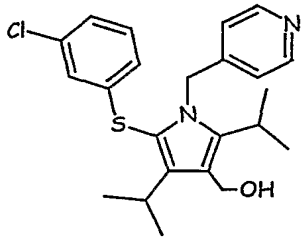
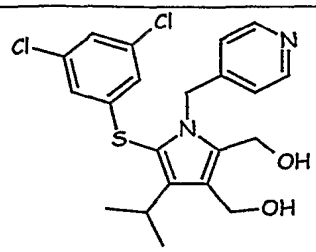
In the assay, compounds of the formulas I range in activity from an IC_{50} of about 0.5 to about 5000 nM, with preferred compounds having a range of activity from about 0.5 to about 750 nM, more preferably about 0.5 to 300 nM, and most preferably about 0.5 to 50 nM.

Structure	RT IC_{50}/nM	HIV IC_{50}/nM
	79	17.5

	930	580
	4120	ND
	260	11.5
	5430	ND
	86	69

	493	407
	198	32
	117	44
	91	16
	90	ND

	658	91
	289	183
	972	ND
	2450	ND
	287	49
	150	22

	125	94
	283	84
	33	16
	43	11
	272	110
	60	10

ND = not determined

It will be understood that references herein to treatment extend to prophylaxis as well as to treatment of existing conditions. It will also be understood that references to the treatment of animals includes the treatment of humans as well as other mammals.

In the present specification "comprise" means "includes or consists of" and "comprising" means "including or consisting of".

The features disclosed in the foregoing description, or the following claims, or the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilised for realising the invention in diverse forms thereof.

The pyrrole derivatives provided by the present invention can be used together with a therapeutically inert carrier as medicaments in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally, such as orally, in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, or nasally, e.g. in the form of nasal sprays. They can also be administered rectally, e.g. in the form of suppositories, or parenterally, (e.g. intramuscularly, intravenously, or subcutaneously), for example, in the form of injection solutions.

For the manufacture of pharmaceutical preparations the pyrrole derivatives can be formulated with therapeutically inert, inorganic or organic carriers.

Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules.

Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like.

Suitable carriers for the manufacture of injection solutions are, for example, water, saline, alcohols, polyols, glycerine, vegetable oils and the like. Natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like are suitable carriers for the manufacture of suppositories. The pharmaceutical preparations of the present invention may also be provided as sustained release formulations or other appropriate formulations.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavourants, salts for adjustment of the osmotic pressure, buffers, masking agents or antioxidants.

The pharmaceutical preparations may also contain other therapeutically active agents such as those mentioned above.

The pyrrole derivatives provided by the invention in the treatment of an immune mediated condition or disease, a viral disease, a bacterial disease, a parasitic disease, an inflammatory disease, a hyperproliferative vascular disease, a tumor, or cancer.

The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day in monotherapy and/or in combination therapy are commonly administered from about 1 to 5 times per day. A typical preparation will contain from about 5% to 95% active compound (w/w) . The daily dosage can be administered as a single dosage or in divided dosages.

The pyrrole derivatives provided by the present invention or the medicaments thereof may be for use in monotherapy and/or combination therapy, i.e. the treatment may be in conjunction with the administration of one or more additional therapeutically active substance(s). When the treatment is combination therapy, such administration may be concurrent or sequential with respect to that of the pyrrole derivatives of the present invention. Thus, concurrent administration, as used herein, includes administration of the agents in conjunction or combination, together, or before or after each other.

It will be understood that references herein to treatment extend to prophylaxis as well as to treatment of existing conditions. Treatment of a disease or condition, as used herein, also includes preventing, inhibiting, regressing, reversing, alleviating or relieving the disease or condition, or the clinical symptoms thereof. The term "subject" as used herein refers to animals, including humans and other mammals.

With regard to the starting materials that are known compounds some of these may be purchased from commercial suppliers. Other starting materials that are known and their analogues can be prepared by methods well known in the art. Examples of compounds available from commercial suppliers, and citations to the synthesis of other compounds and their analogues are provided in the following:

The described NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer with the probe temperature set at 300 K.

The mass spectra indicated by "(M+; EI)", were recorded under electron impact conditions (EI), on a THERMOQUEST MAT95 S with a source temperature of 200°C. Other mass spectra were recorded under electrospray ionization spectra (ESI) conditions, on one of the following machines:

a) THERMOQUEST SSQ 7000 [Solvent 0.085% TFA in 90% Acetonitrile/water; flow rate 100 microliters/minute; capillary 250°C; spray voltage 5KV; sheath gas 80 psi], or

b) LC-MS system (liquid chromatograph coupled to mass spectrum) THERMOQUEST TSQ 7000 ELECTROSPRAY or MICROMASS PLATFORM ELECTROSPRAY [Solvent 0.1% TFA in water or 0.085% TFA in 90% acetonitrile/ water or 0.085% TFA in acetonitrile].

In the following examples the abbreviations used have the following significations:

min	minute(s)
h	hour(s)
d	day(s)
EDAC	1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride
HOBt	1-Hydroxybenzotriazole

The following examples illustrate the present invention:

Example 1

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol

A solution containing 0.1g of ethyl 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1-pyridin-4-yl-1H-pyrrole-3-carboxylate in 0.5 ml of anhydrous diethyl ether was added dropwise to 0.54 ml of a 1M solution of lithium aluminium hydride which was stirred and cooled at 0-5°C. The mixture was stirred at 5°C for 1 h then at room temperature for 1 h. The mixture was cooled again to 5°C and quenched with saturated ammonium chloride solution, then extracted three times with 10ml of ethyl acetate. The combined extracts were washed with 10ml of brine, then dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using methanol/dichloromethane (1:19) for the elution to give 70mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol as a pale orange gum. Mass spectrum (ESI) m/z 421 $[M+H]^+$. ^1H NMR ($CDCl_3$) 1.31 (d, 6H), 2.21 (s, 3H), 3.24 (m, 1H), 4.66 (s, 2H), 5.10 (s, 2H), 6.68 (d, 2H), 6.74 (m, 2H), 6.98 (t, 1H), 8.44 (m, 2H).

The starting material ethyl 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1-pyridin-4-yl-1H-pyrrole-3-carboxylate was prepared as follows:

(A) A solution containing 18.8g of N-tert.-butoxycarbonylglycine in 180ml of anhydrous dichloromethane was stirred under nitrogen and cooled at 0-5°C while 11.5g of N,O-dimethylhydroxylamine hydrochloride, 27.1g of N-ethylmorpholine and 22.5g of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride were added. The mixture was allowed to warm slowly to room temperature and stirred for 16 h. The mixture was washed twice with 150ml of 1M hydrochloric acid, and 150ml of saturated sodium hydrogen carbonate then dried over anhydrous sodium sulphate, filtered and evaporated to give 22.5g of N-tert.-butoxycarbonylglycine N-methyl-N-methoxyamide as a white solid which was used without further purification.

(B) A solution of 10.9g of N-tert.-butoxycarbonylglycine N-methyl-N-methoxyamide in 300ml of anhydrous tetrahydrofuran and 100ml of anhydrous diethyl ether was cooled at 0-5°C while 100ml of a 2M solution of isopropyl magnesium chloride in tetrahydrofuran was added slowly. The mixture was stirred at 0-5°C for 4 h then poured into 1.5 litre of 1M hydrochloric acid. The product was extracted with three portions of 500ml diethyl ether. Combined extracts were washed with 500ml brine then dried over anhydrous magnesium sulphate, filtered and evaporated to give 8.38g of 4-tert.-butoxycarbonylamino-2-methyl-3-butanone as a colourless oil which was used without further purification.

(C) 7.03g of 4-tert.-butoxycarbonylamino-2-methyl-3-butanone was added to 80ml of an ice cold 4M solution of hydrogen chloride in ethyl acetate. The solution was stirred at 0-5°C for 1 h during which time a precipitate separated. The mixture was evaporated under reduced pressure and the residue triturated with anhydrous ether. The white solid product was filtered off, washed with anhydrous diethyl ether and dried to give 4.14g of 4-amino-2-methyl-3-butanone hydrochloride.

(D) A solution containing 0.32g of 4-amino-2-methyl-3-butanone hydrochloride, 0.33g of ethyl acetoacetate and 0.28g of sodium acetate in 2ml of 75% acetic acid was heated at 100°C for 1.5 h. The mixture was poured into 10ml of water and extracted three times with 10ml of diethyl ether. Combined extracts were washed three times with 10ml of saturated sodium hydrogen carbonate and with 10ml of brine then dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using dichloromethane for the elution to give 0.15g of ethyl 4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate. Recrystallisation from isohexane gave analytically pure material of melting point 67-68.5°C; mass spectrum (EI) m/z 195 $[M]^+$.

(E) A solution of 1.03g of ethyl 4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate in 27ml of anhydrous dichloromethane was treated with 2.06g of N-iodosuccinimide and stirred at room temperature for 2 h. The mixture was diluted with a further 50ml of

dichloromethane and washed with 50ml of saturated sodium thiosulphate solution and 50ml of saturated sodium hydrogen carbonate solution. The dichloromethane extract was dried over anhydrous sodium sulphate then filtered and evaporated. The residue was triturated with 50ml of petroleum ether (bp 40-60°C). The orange solid product was filtered off and dried to give 1.32g of ethyl 5-iodo-4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate; mass spectrum (ESI) m/z 322 $[M+H]^+$.

(F) A solution of 1.3g of ethyl 5-iodo-4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate in 8ml of anhydrous dimethyl sulphoxide was stirred under nitrogen at room temperature and 39mg of lithium hydride added followed after 10min by 0.86g of bis-(3,5-dichlorophenyl)disulphide. The mixture was stirred under nitrogen and heated at 60°C for 6 h then stood at room temperature for 16 h. The mixture was diluted with 150ml of water and extracted three times with 75ml of diethyl ether. Combined extracts were washed with 50ml of brine then dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown gum which crystallised. Recrystallisation from methylcyclohexane gave 0.66g of ethyl 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate of melting point 148-151°C; mass spectrum (EI) m/z 371$[M]^+$.

(G) A solution of 0.1g of ethyl 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1H-pyrrole-3-carboxylate in 2ml of anhydrous tetrahydrofuran was stirred at room temperature under nitrogen and treated with 65mg of 4-bromomethylpyridine hydrobromide, 5mg of tetra-n-butylammonium bromide and 24mg of powdered sodium hydroxide. The mixture was stirred at room temperature for 20 h then diluted with 20ml of water and extracted three times with 10ml of ethyl acetate. Combined extracts were washed with 10ml of brine, then dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using ethyl acetate/isohexane (1:1) for the elution to give 0.104g of ethyl 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1-pyridin-4-yl-1H-pyrrole-3-carboxylate as a colourless gum. Mass spectrum (ESI) m/z 463 $[M+H]^+$. ^1H NMR ($CDCl_3$) 1.32 (d, 6H), 1.40 (t, 3H), 2.45 (s, 3H), 3.61 (m, 1H), 4.34 (q, 2H), 5.16 (s, 2H), 6.69 (d, 2H), 6.76 (m, 2H), 7.01 (t, 1H), 8.47 (m, 2H).

Example 2

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxaldehyde

A solution of 0.2g of 3,5-dichlorophenylsulphanyl-3-hydroxymethyl-4-isopropyl-2-methyl-1-pyridin-4-yl-pyrrole and 7.5mg of 2,2,6,6-tetramethylpiperidine N-oxide in

0.5ml of anhydrous dichloromethane was treated with 0.17g of iodobenzene diacetate. The mixture was stirred at room temperature for 4 h then diluted with 10 ml of dichloromethane and washed with 10ml of saturated sodium thiosulphate and 10ml of saturated sodium hydrogen carbonate, then dried over anhydrous sodium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using methanol/dichloromethane (1:49) for the elution to give 50mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxaldehyde as a gum. Mass spectrum (ESI) m/z 419$[M+H]^+$. ^1H NMR ($CDCl_3$) 1.36 (d, 6H), 2.53 (s, 3H), 3.46 (m, 1H), 5.16 (s, 2H), 6.69 (d, 2H), 6.74 (m, 2H), 7.02 (t, 1H), 8.47 (m, 2H), 10.21 (s, 1H).

Example 3

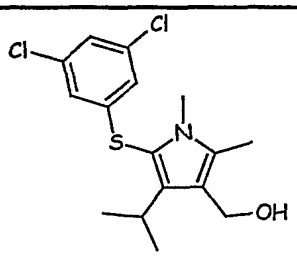
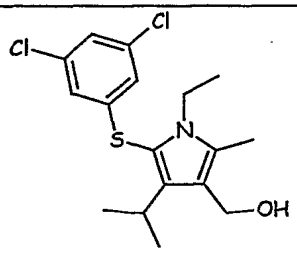
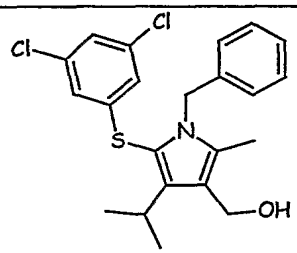
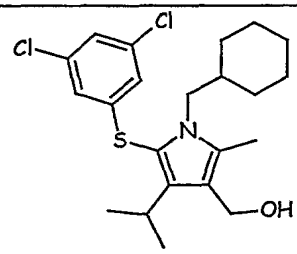
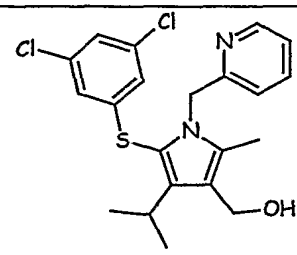
5-(3,5-Dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol

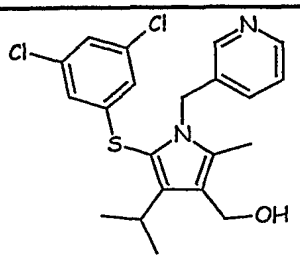
A solution of 90mg of 5-(3,5-dichlorophenylsulphanyl)-4-isopropyl-2-methyl-1-pyridin-4-yl-1H-pyrrole-3-carboxaldehyde in 1ml of anhydrous tetrahydrofuran was stirred under nitrogen and cooled at 0-5°C while 0.21ml of a 1.4M solution of methyl magnesium bromide in toluene/tetrahydrofuran (75:25) was added dropwise. The mixture was stirred at 0-5°C for 2 h then diluted with 10ml of saturated ammonium chloride solution and extracted twice with 10ml of ethyl acetate. Combined extracts were washed with 10ml of brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using methanol/dichloromethane (1:19) for the elution to give 19mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol as a gum. Mass spectrum (ESI) m/z 435 $[M+H]^+$. ^1H NMR ($CDCl_3$) 1.26 (d, 3H), 1.29 (d, 3H), 1.55 (d, 3H), 1.77 (bs, 1H), 2.30 (s, 3H), 3.30 (m, 1H), 5.08 (s, 2H), 5.25 (q, 1H), 6.67 (d, 2H), 6.71 (m, 2H), 6.97 (t, 1H), 8.43 (m, 2H).

Examples 4-9

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (commercially available from Fluka or Aldrich), the compounds shown in table 2 were also prepared:

Table 2

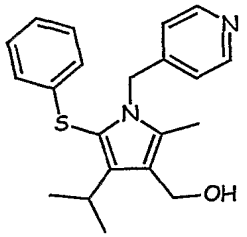
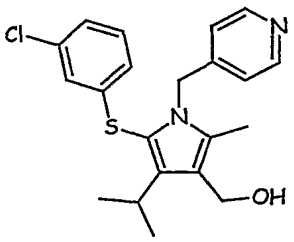
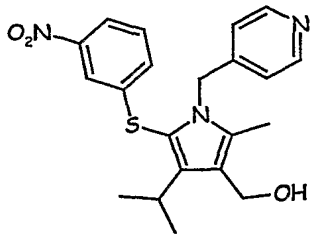
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
4		5-(3,5-Dichlorophenylthio)-4-isopropyl-1,2-dimethyl-1H-pyrrole-3-methanol	344
5		5-(3,5-Dichlorophenylthio)-1-ethyl-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	356
6		1-Benzyl-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	420
7		1-(Cyclohexylmethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	
8		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(2-pyridyl)methyl]-1H-pyrrole-3-methanol	421

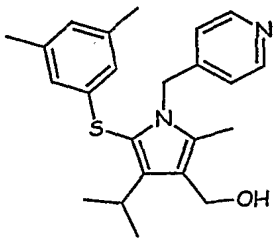
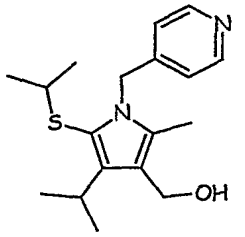
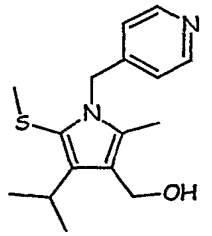
9		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol	421

Examples 10-15

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia), the compounds shown in table 3 were also prepared:

Table 3

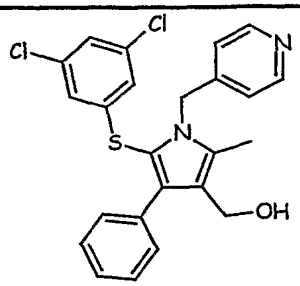
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
10		4-Isopropyl-2-methyl-5-phenylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	352
11		5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	387
12		4-Isopropyl-2-methyl-5-(3-nitrophenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	399

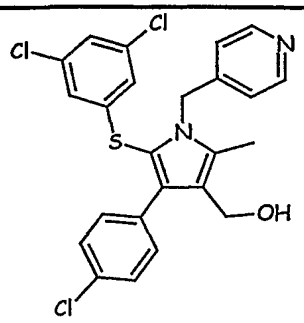
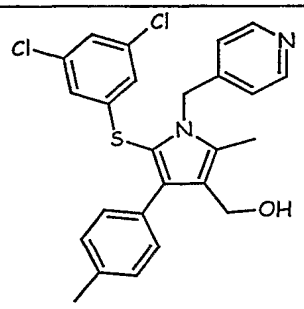
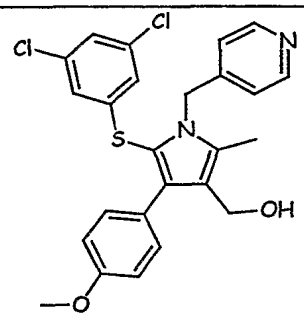
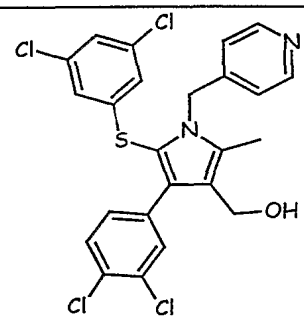
13		5-(3,5-Dimethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	380
14		4-Isopropyl-5-isopropylthio-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	
15		4-Isopropyl-2-methyl-5-methylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	

Examples 16-20

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia), the compounds shown in table 4 were also prepared:

Table 4

Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
16		5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	455

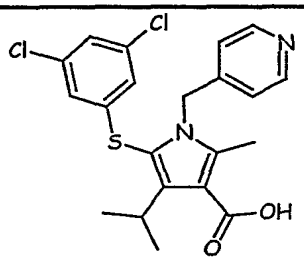
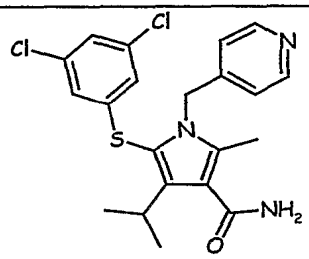
17		4-(4-Chlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	490
18		5-(3,5-Dichlorophenylthio)-2-methyl-4-(4-methylphenyl)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	469
19		5-(3,5-Dichlorophenylthio)-4-(4-methoxyphenyl)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	485
20		4-(3,4-Dichlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	524

Examples 21-22

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) transferred to a compound of the formula XI, the compounds shown in table 5 were also prepared via hydrolysis of XI

when R = tert.-butyl (example 21) or via intermediate XII (Scheme 3) where R^{5a} = amino (example 22):

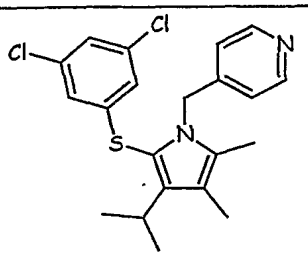
Table 5

Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
21		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid	435
22		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	434

Examples 23

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) transferred to a compound of the formula Ic, the compounds shown in table 6 were prepared by mesylation reaction with for example CH_3SO_2Cl and Et_3N followed by a reduction reaction with for example Zn/acetic acid (as described in J. Org. Chem. 1997, 62, 9223):

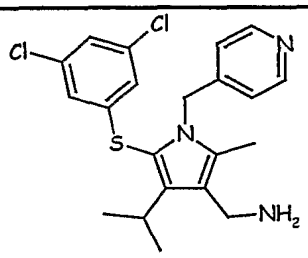
Table 6

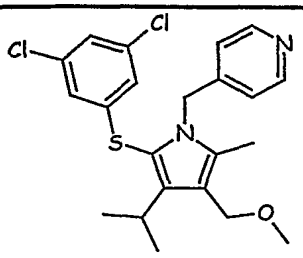
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
23		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4,5-dimethyl-1H-pyrrol-1-yl]methyl]pyridine	405

Examples 24-25

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) the compounds shown in table 7 were prepared from 1a by conversion of alcohol to chloride then displacement of chloride with azide and finally reduction of azide with hydrogen (example 24) or via nucleophilic substitution reaction with a methoxide anion (example 25) of the chloride of the alcohol of the formula Ia.

Table 7

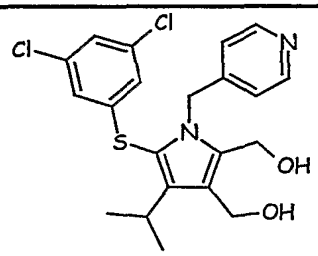
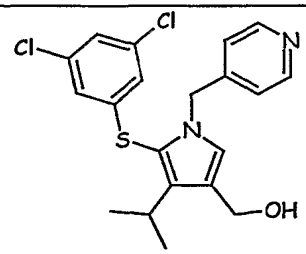
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
24		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylamine	420

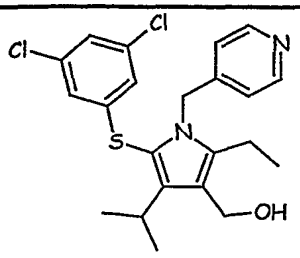
25		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1H-pyrrol-1-yl]methyl]pyridine	435

Examples 26-28

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) the compounds shown in table 8 were also prepared up to intermediate V which was then taken forward via Reaction Scheme 6. Example 28 was prepared according to Scheme 1 where R = ethyl in intermediate VI.

Table 8

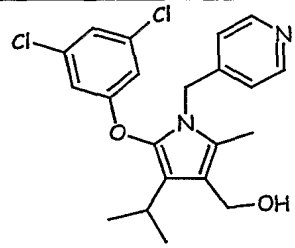
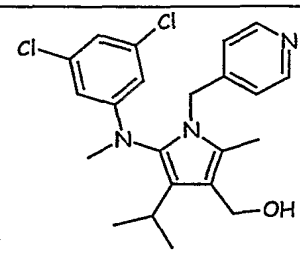
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
26		5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	437
27		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	

28		5-(3,5-Dichlorophenylthio)-2-ethyl-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	435

Examples 29-30

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) the compounds shown in table 9 were also prepared. The examples are prepared by bromination of the compounds of the formula VII to the corresponding 2-substituted bromopyrrole which is then further reacted with the corresponding neutral oxygen nucleophile in the presence of Et_3N to obtain the corresponding oxy pyrrole derivative (example 29). To obtain the corresponding N-substituted pyrrole derivatives (example 30), the above-mentioned 2-substituted bromopyrrole is reacted with a primary or a secondary amine.

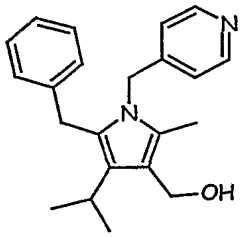
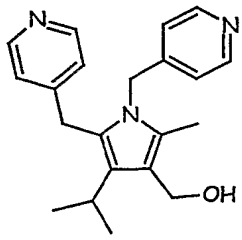
Table 9

Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
29		5-(3,5-Dichlorophenoxy)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	
30		5-[(3,5-Dichlorophenyl)methylamino]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	

Examples 31-32

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ia) the compounds shown in table 10 were also prepared. The examples are prepared by coupling reaction of the corresponding compounds of the formula 5a with the corresponding β-keto ester of the formula VI to obtain examples 31-32.

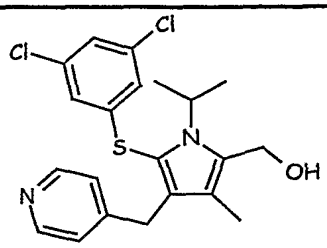
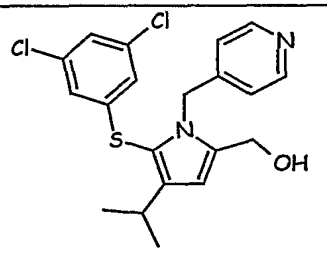
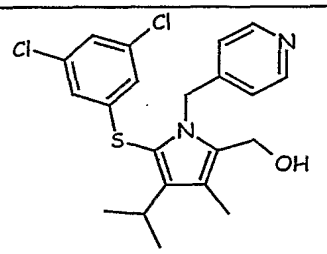
Table 10

Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
31		5-Benzyl-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	334
32		4-Isopropyl-2-methyl-1,5-bis[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	

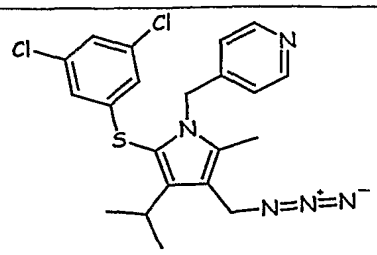
Examples 33-35

In a manner analogous to that described in example 1-3, starting with N-tert.-butoxycarbonylglycine (prepared as described in example Ic) example 34 was made according to reaction scheme 9.

Table 11

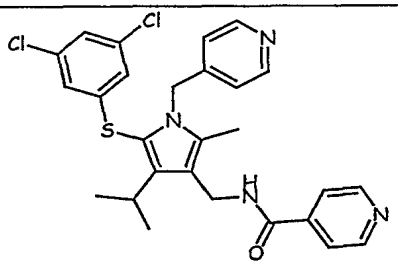
Example	Structure	Name	Mass Spectrum (m/z ES, +ve ion)
33		5-(3,5-Dichlorophenylthio)-1-isopropyl-3-methyl-4-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	
34		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	407
35		5-(3,5-Dichlorophenylthio)-4-isopropyl-3-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	

Example 93

Ex.	STRUCTURE	SYSTEMATIC NAME	MS
93		4-[[3-(Azidomethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridine	446

To a solution of 200mg of 4-[[3-(Chloromethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridine in 5mL of DMF was added 137mg of sodium azide. The mixture was stirred at room temperature for 18 h. The yellow solution was quenched with saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:2) then ethyl acetate for the elution to give 129mg as a yellow oil. Mass spectrum (ESI) m/z 446 [M+H]+. Mass spectrum (ESI) m/z 446 $[M+H]^+$.

Example 76

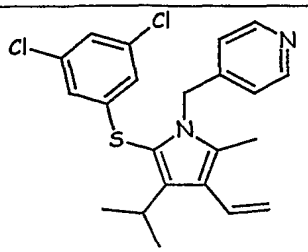
76		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-4-pyridineacetamide	525

To a solution of 70mg of 5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylaminein 3mL of dichloromethane was added 30mg of isonicotinyl chloride and 50mg of triethylamine. The mixture was stirred at room temperature for 18 h then quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was preabsorbed onto silica then purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9 then 1:4) for the elution to give 50mg as a cream solid. Mass spectrum (ESI) m/z 525 $[M+H]^+$.

The starting material 5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylaminewas prepared as follows:

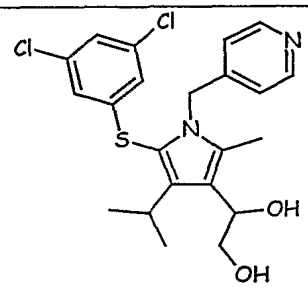
To a solution of 2.33g of 4-[[3-(Azidomethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridinein 100mL of ethyl acetate was added 100mg of 10% Pd on carbon catalyst. The mixture was hydrogenated for 1.5 h. The mixture was filtered and evaporated to give 2.2g of a yellow oil. Mass spectrum (ESI) m/z 446 $[M+H]^+$.

Example 95

95		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-4-vinyl-1-pyrrolyl]methyl]pyridine	417

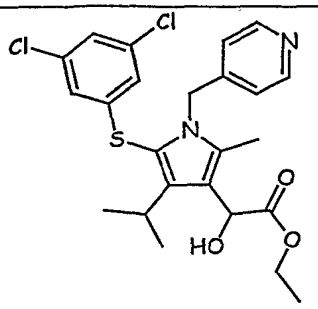
A solution of 90mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol in 3mL of DMSO was heated at 160°C for 30 min. The brown solution was cooled to room temperature then quenched with saturated sodium bicarbonate solution and extracted with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 up to 1:1) then ethyl acetate for the elution to give 28mg as a oil. Mass spectrum (ESI) m/z 417 $[M+H]^+$.

Example 96

96		1(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-1,2-ethanediol	451

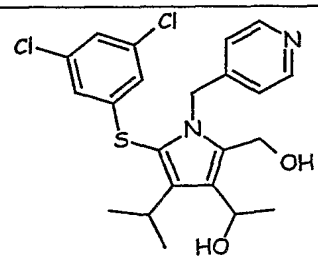
To a degassed solution of 61mg of 4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-4-vinyl-1-pyrrolyl]methyl]pyridine in 20mL of dioxane and 3.5mL of water was added 26mg of N-methyl morpholine N-oxide and 4mg of osmium tetroxide. The reaction was kept dark by covering with aluminium foil and stirred at room temperature for 24 h. The solution was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown gum which solidified on addition of ethyl acetate to give 29mg of a brown solid. This solid was further purified by HPLC to give 0.4mg of the product. Mass spectrum (ESI) m/z 451 $[M+H]^+$.

Example 75

75		[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-2-methyl-1-pyridin-4-ylmethyl-1H-pyrrol-3-yl]-hydroxy-acetic acid ethyl ester	493

To a solution of 140mg of [5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-2-methyl-1-pyridin-4-ylmethyl-1H-pyrrol-3-yl]-oxo-acetic acid ethyl ester in 5mL of ethanol was added 54mg of sodium borohydride. The mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9 up to 1:4) for the elution to give 22mg as a white foam. Mass spectrum (ESI) m/z 493 $[M+H]^+$.

Example 107

107		5-(3,5-Dihlorophenylthio)-2-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol	451

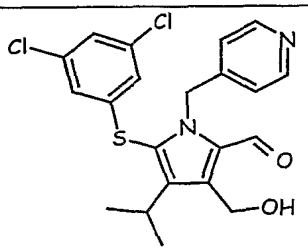
To a solution of 120mg of 1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]ethanone in 3 mL of ether at 0°C was added 1.25mL of a 1M solution of lithium aluminium hydride in ether. The reaction was allowed to warm to room temperature over 30 min. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using ethyl acetate for the elution to give 35mg which required further purification by HPLC giving the desired product and the de-chlorinated derivative 5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-(2-ethanol). Mass spectrum (ESI) m/z 451 $[M+H]^+$.

The starting material 1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]ethanone was prepared as follows:

(A) A mixture of 2.45g of pent-2-yn-4-one-oate ethyl ester, 3.19g of 1-amino-3-methylbutan-2-one hydrobromide and 1.44g of sodium acetate were dissolved in 88ml of ethanol and heated at reflux for 30 min. Then 8ml of concentrated hydrochloric acid were added and reflux continued. After 1 h the solvent was evaporated and the residue partitioned between saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9 up to 1:4) for the elution to give 750mg of 4-isopropyl-1H-pyrrole-3-ethanone-2-ethyl ester as a white foam. Mass spectrum (ESI) m/z 223 $[M+H]^+$.

(B) Iodination, sulfuration and alkylation to give 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanone-2-ethyl ester were all carried out according to procedures described for examples from Scheme 1.

Example 108

108		5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehyde	438

To a solution of 88mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-3-ethyl ester-1-[(4-pyridyl)methyl]-1H-2-[N-methyl-N-methoxyamide]-pyrrole in 5mL of THF at 0°C was added 0.33mL of a 1M solution of lithium aluminium hydride in ether. The reaction was allowed to warm to room temperature over 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:2) for the elution to give the desired product, 29mg of an oil, and 6mg of 5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-dicarboxaldehyde as an oil. Mass spectrum (ESI) m/z 438 $[M+H]^+$.

The starting material 5-(3,5-dichlorophenylthio)-4-isopropyl-3-ethyl ester-1-[(4-pyridyl)methyl]- 2-[N-methyl-N-methoxyamide]-1H-pyrrole was prepared as follows:

(A) A mixture of 0.5g of amino-3-methylbutan-2-one hydrochloride, 0.58ml of diethylacetylene dicarboxylate and 295mg of sodium acetate were refluxed in 18ml of ethanol for 10 min. A few drops of concentrated hydrochloric acid were then added and the mixture boiled further. The reaction was cooled to room temperature then partitioned between dichloromethane and ice water. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9, 1:6 then 1:4) then ethyl acetate for the elution to give 323mg of 4-isopropyl-2,3-dicarboxylate ethyl ester as a yellow oil. Mass spectrum (ESI) m/z 253 $[M+H]^+$.

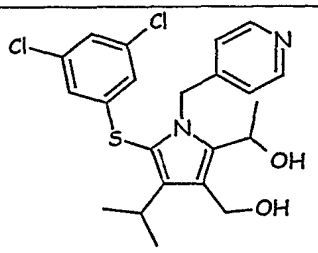
(B) Iodination, sulfuration and alkylation to give 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-bisethyl ester were all carried out according to procedures described for examples from Scheme 1.

(C) To a solution of 462mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-bisethyl ester in 12mL of ethanol was added 50mg of potassium hydroxide. The mixture was refluxed for 18 h then a further 20mg of potassium hydroxide was added and refluxing continued for 3 h. The solvent was evaporated and the residue partitioned between ethyl acetate and dilute hydrochloric acid. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was triturated with ether to give 417mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-3-ethyl ester-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxylic acid as an orange foam. Mass spectrum (ESI) m/z 493 $[M+H]^+$.

(D) To a solution of 417mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-3-ethyl ester-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxylic acid in 10mL of dichloromethane was added 243mg of EDAC, 171mg of HOBt, 124mg of N,N-dimethyl hydroxylamine then finally 0.33mL of N-ethyl morpholine. The reaction mixture was stirred at room temperature for 1 h. The orange solution was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 233mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-3-

ethyl ester-1-[(4-pyridyl)methyl]- 2-[N-methyl-N-methoxyamide]-1H-pyrrole as a yellow oil. Mass spectrum (ESI) m/z 535 $[M+H]^+$.

Example 110

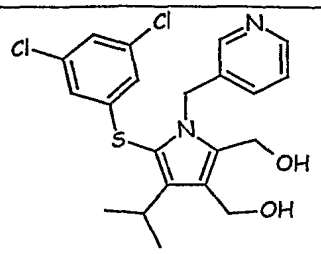
110		5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-ethanol	451

To a solution of 60mg of 5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehydein 1mL of THF was added 0.1mL of a 3M solution of methyl magnesium iodide in diethyl ether. The mixture was stirred at room temperature under nitrogen for 1 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using ethyl acetate for the elution to give 22mg of a gum. Mass spectrum (ESI) m/z 451 $[M+H]^+$.

The starting material 5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehyde was prepared as follows:

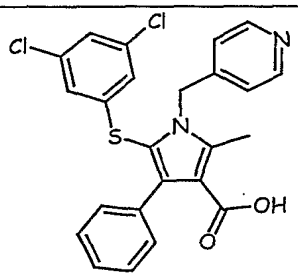
To a solution of 371mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-3-ethyl ester-1-[(4-pyridyl)methyl]- 2-[N-methyl-N-methoxyamide]-1H-pyrrole in 10mL of THF at 0°C was added 1.4mL of a 1M solution of lithium aluminium hydride in ether. The mixture was stirred for 30 min then quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using ethyl acetate for the elution to give 223mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol-2-carboxaldehyde as a gum. Mass spectrum (ESI) m/z 434 $[M+H]^+$.

Example 111

111		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(3-pyridyl]methyl]-1H-pyrrole-2,3-dimethanol	437

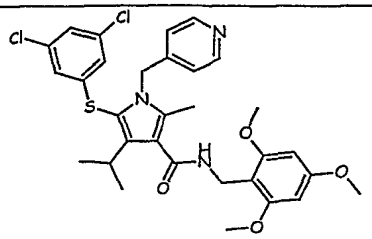
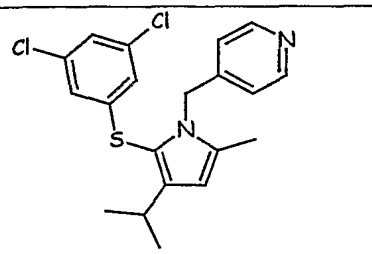
To a 1M solution of lithium aluminium hydride in ether at 0°C, under nitrogen, was added 70mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-bisethyl ester as a solution in 3mL of ether. The mixture was stirred for 1 h then quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9 then 1:4) for the elution to give 16mg of a gum. Mass spectrum (ESI) m/z 437 $[M+H]^+$.

Example 117

117		5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid trifluoroacetate (1:1)	469

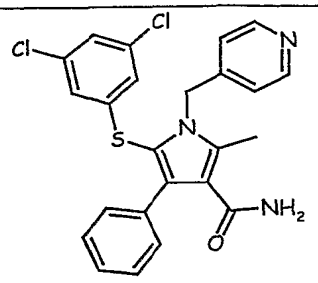
To a solution of 243mg of 5-(3,5-dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-*tert*butyl ester in 6ml of dichloromethane was added 6ml of trifluoroacetic acid at room temperature. The mixture was stirred for 1 h then evaporated and the residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:1) for the elution to give 155mg of a foam. Mass spectrum (ESI) m/z 469 $[M+H]^+$.

Example 115

115		5-(3,5-Dichlorophenylthio)-N-(2,4,6-trimethoxybenzyl)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	614
115a		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine	391

To a solution of 160mg of 5-(3,5-Dichlorophenylthio)-2-methyl-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid in 10ml of dichloromethane was added 60mg of EDAC, 40mg of HOBt, 68mg of 2,4,6-trimethoxybenzylamine hydrochloride and 0.11ml of N-ethyl morpholine. The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 29mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole as an oil, mass spectrum (ESI) m/z 391 $[M+H]^+$ and 114mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-N-[(2,4,6-trimethoxy)benzyl]-carboxamide as an oil, mass spectrum (ESI) m/z 614 $[M+H]^+$.

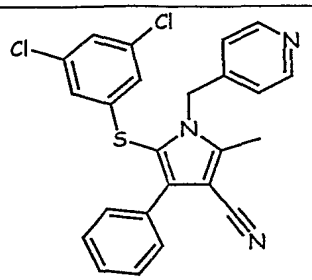
Example 118

118		5-(3,5-Dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	468

To a solution of 110mg of 5-(3,5-Dichlorophenylthio)-N-(2,4,6-trimethoxybenzyl)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamidein 4ml of

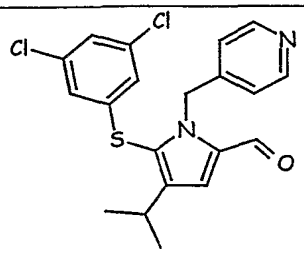
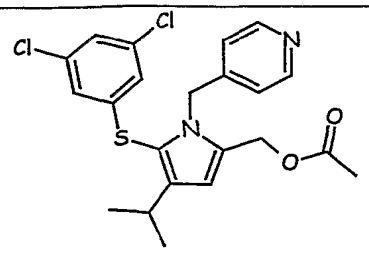
dichloromethane was added 3ml of trifluoroacetic acid at room temperature. The mixture was stirred for 1 h then evaporated and the residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:9 then 1:4) for the elution to give 26mg of a white solid. Mass spectrum (ESI) m/z 468 $[M+H]^+$.

Example 119

119		5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carbonitrile	450

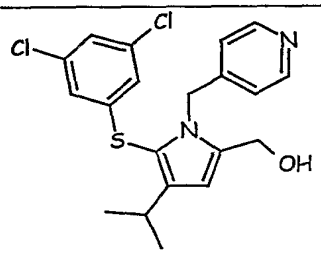
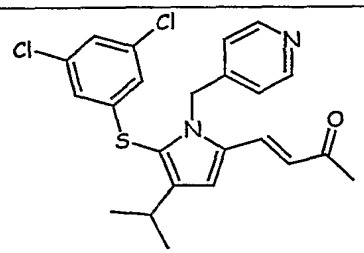
To a solution of 17mg of 5-(3,5-Dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide in toluene was added 22mg of Lawessons reagent. The mixture was refluxed for 1 h then cooled to room temperature. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 13mg of a gum. Mass spectrum (ESI) m/z 450 $[M+H]^+$.

Example 113

113a		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carbaldehyde	405
113		[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl acetate	447

To a solution of 160mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole in 3ml of acetic acid was added 200mg of lead tetraacetate over 30 min. After stirring for 2 h at room temperature a further 100mg of lead tetraacetate was added and the mixture stirred for 18 h. After this time a further 100mg of lead tetraacetate was added and the mixture stirred for 18 h. The reaction was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 23mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carbaldehyde, mass spectrum (ESI) m/z 405 $[M+H]^+$, as a brown oil and 51mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-acylmethanol as an impure yellow foaming oil, Mass spectrum (ESI) m/z 447 $[M+H]^+$.

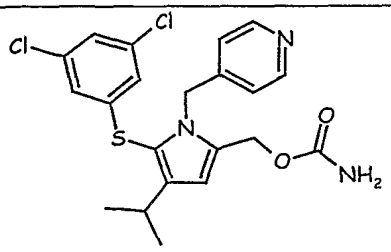
Examples 112, 114

112		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	407
114		4-[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-pyrrol-2-yl]-but-3-en-2-one	445

To a solution of 51mg of the impure 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-acylmethanol in 4ml of 50% aqueous acetone was added 50mg of powdered potassium hydroxide. The mixture was stirred at room temperature for 2 h. The reaction was quenched with water and extracted with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 8mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol as a yellow gum, mass spectrum (ESI) m/z 407 $[M+H]^+$, and 9mg of 5-(3,5-dichlorophenylthio)-4-isopropyl-1-

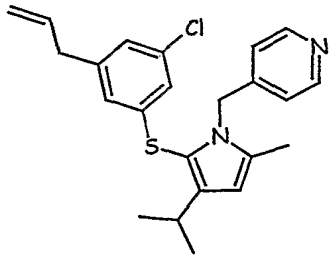
[(4-pyridyl)methyl]-1H-pyrrole-2-[4'-but-3-en-2-one] as a yellow gum, mass spectrum (ESI) m/z 445 $[M+H]^+$.

Example 130

130		[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl carbamate	450

To a solution of 103mg of 5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol in 3ml of dichloromethane was added 57mg of trichloroacetyl isocyanate dropwise at 0°C. The mixture was stirred at 0°C for 2 h then evaporated. To the residue was added 2ml of methanol, 1ml of water and 103mg of potassium carbonate at 0°C. The mixture was warmed to room temperature and stirred for 2 h. After this time the solution was homogenous and orange in colour. The reaction was quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4) for the elution to give 27mg of a white solid. Mass spectrum (ESI) m/z 450 $[M+H]^+$.

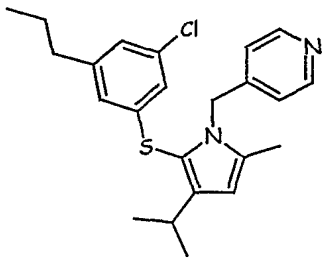
Example 132

132		4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridine	397

To a solution of 80mg of 4-[[2-(3-Bromo-5-chlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine in 5ml of dimethoxyethane was added 156ul of allyltributyltin and 60mg of tetrakis(triphenylphosphine) palladium. The mixture was

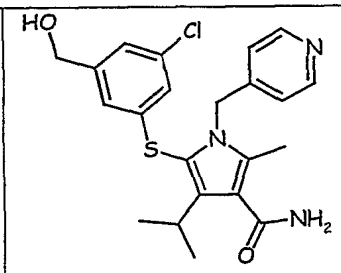
heated to 70°C for 18 h. The mixture was directly purified by flash chromatography on silica gel using methanol/dichloromethane (1:19) for the elution to give 40mg of a white solid. Mass spectrum (ESI) m/z 397 $[M+H]^+$.

Example 133

133		4-[[2-(3-Chloro-5-propylphenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine	399

To a solution of 10mg of 4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridine in 5ml of warm ethanol was added 1mg of 10% palladium on carbon. The mixture was hydrogenated for 10 min then filtered through a pad of celite. The filtrate was evaporated to dryness to give 10mg of a white solid. Mass spectrum (ESI) m/z 399 $[M+H]^+$.

Example 135

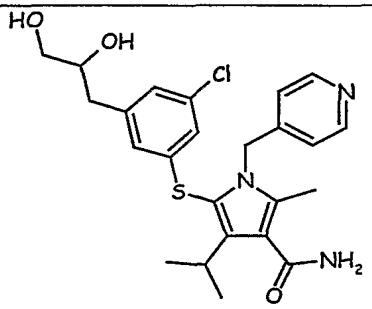
135		5-[3-Chloro-5-(hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	430

To a solution of 25mg of 5-[3-Chloro-5-(carboxaldehyde)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide in 5ml of methanol was added 3mg of sodium borohydride. The mixture was stirred at room temperature for 2 h. A further 3mg of sodium borohydride was then added and the mixture stirred for 1 h. To the reaction was added 150mg of silica gel and the solvents evaporated. The product, absorbed onto silica, was purified by flash chromatography on silica gel using methanol/dichloromethane (1:9) for the elution to give 15mg of a white solid. Mass spectrum (ESI) m/z 430 $[M+H]^+$.

The starting material 5-[3-Chloro-5-(carboxaldehyde)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide was prepared as follows:

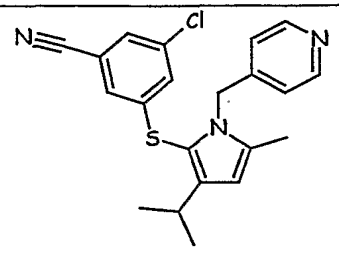
To a solution of 5-[3-Chloro-5-vinyl phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide in 20ml of THF, 10ml of water and 6ml of *tert*butanol was added 290mg of osmium tetroxide. The mixture was stirred at room temperature for 30 min and 330mg of sodium periodate added. After 2 h 60mg of the product was precipitated as a white solid by addition of ethyl acetate/water. Mass spectrum (ESI) m/z 425 $[M+H]^+$.

Example 127

127		5-[3-Chloro-5-(2(RS),3-dihydroxypropyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	474

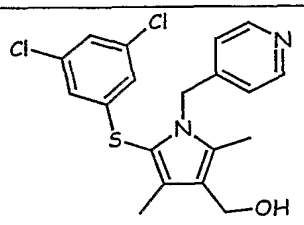
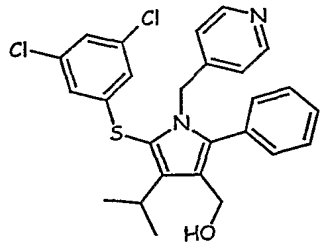
To a solution of 30mg of 4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridinein 7.5ml of THF, 4ml of water and 1ml of *tert.*-butanol was added 18mg of osmium tetroxide. The mixture was stirred at room temperature for 30 min and 20mg of sodium periodate added. After 2 h 15mg of the product was precipitated as a white solid by addition of diethyl ether. Mass spectrum (ESI) m/z 474 $[M+H]^+$.

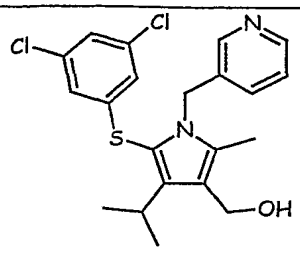
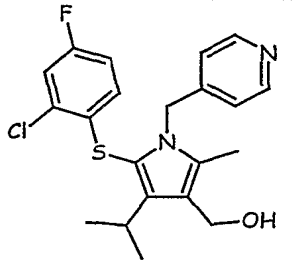
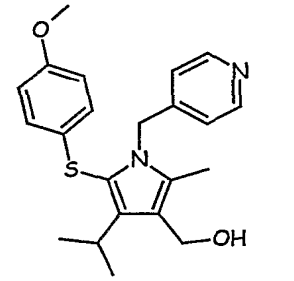
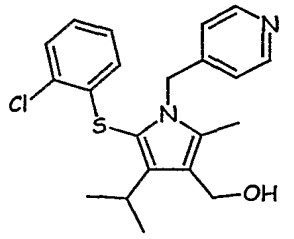
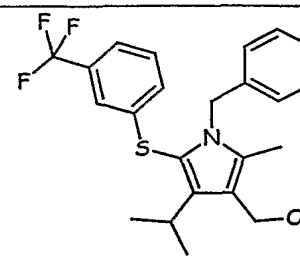
Example 141

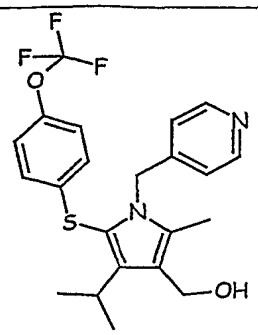
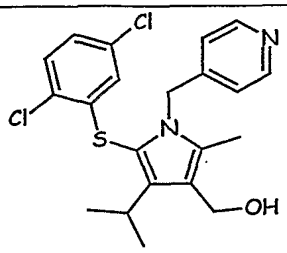
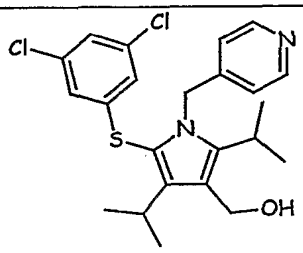
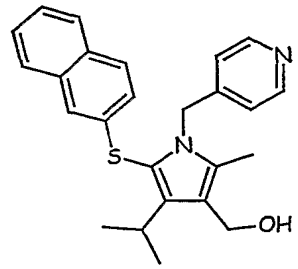
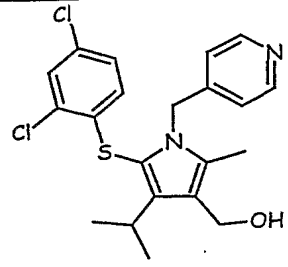
141		3-Chloro-5-[3-isopropyl-5-methyl-1-[(4-pyridinyl)methyl]-1H-pyrrol-2-ylthio]benzonitrile	382

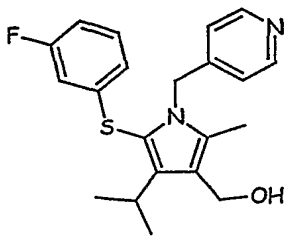
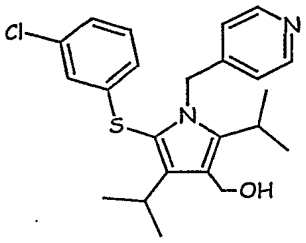
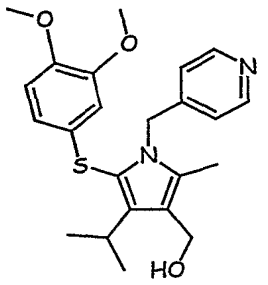
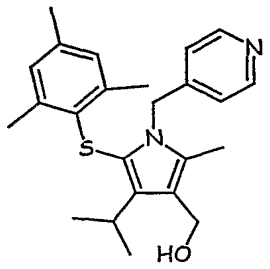
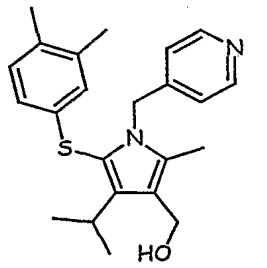
A mixture of 120mg of 4-[[2-(3-Bromo-5-chlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine, 96mg of copper (I) cyanide, 30mg of diphenylphosphino

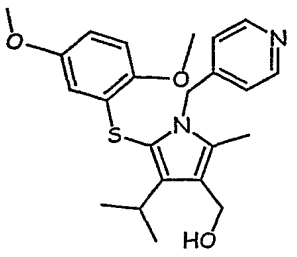
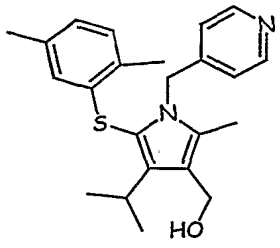
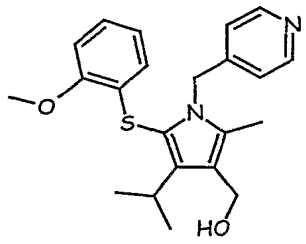
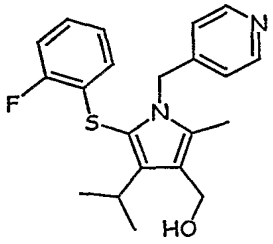
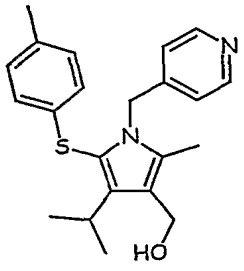
ferrocene, 40mg of tetraethylammonium cyanide and 15mg of bispalladium tris(dibenzylidene acetone) were dissolved on 15ml of dioxane. The mixture was heated to 80°C for 2 h then another 96mg of copper (I) cyanide, 30mg of diphenylphosphino ferrocene, 40mg of tetraethylammonium cyanide and 15mg of bispalladium tris(dibenzylidene acetone) were added and the mixture heated for 72 h. The reaction was then cooled and The mixture was stirred at room temperature for 18 h. The orange solution was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on silica gel using petrol/ethyl acetate (1:4 then 1:2) then ethyl acetate for the elution to give 57mg as an oil which was further purified by HPLC to give 17mg of an oil. Mass spectrum (ESI) m/z 382 $[M+H]^+$.

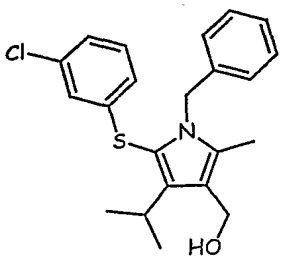
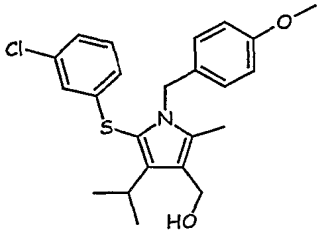
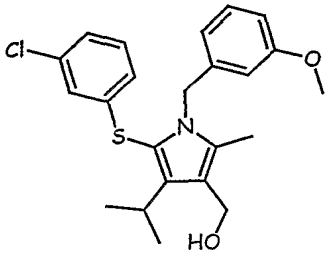
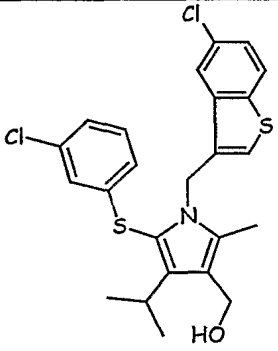
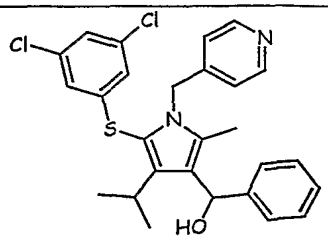
Ex.	STRUCTURE	SYSTEMATIC NAME	Mass Spectrum (m/z ES, +ve ion)	Reaction Scheme
Compounds were prepared analogous to reaction scheme 1:				
36		5-(3,5-Dichlorophenylthio) -2,4-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	393	1 using MeCOCH2NH2
37		5-(3,5-Dichlorophenylthio) -4-isopropyl-2-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	483	1 using PhCOCH2CO2 Et

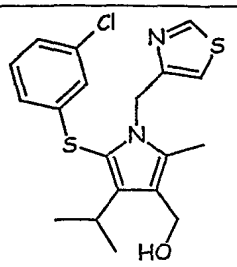
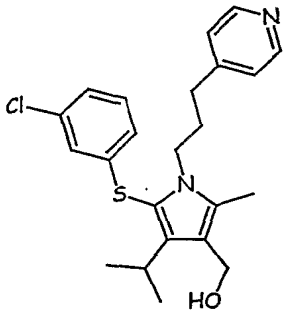
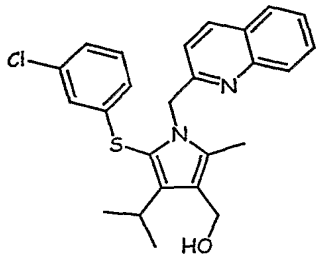
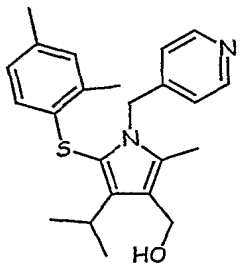
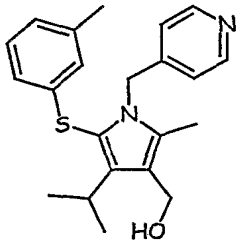
38		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol	421	1 different R1
39		5-(2-chloro-4-fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	404	1 different disulfide
40		4-Isopropyl-5-(4-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	382	1 different disulfide
41		5-(2-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	387	1 different disulfide
42		5-[3-(Trifluoromethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	420	1 different disulfide

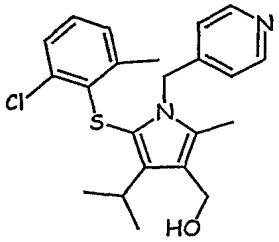
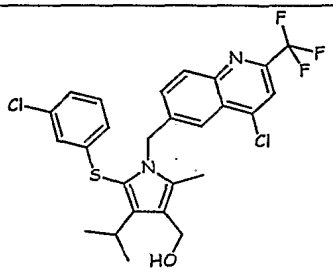
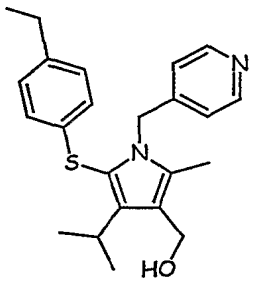
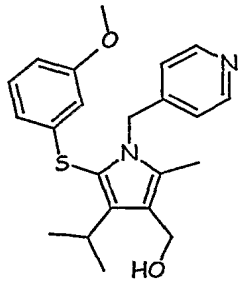
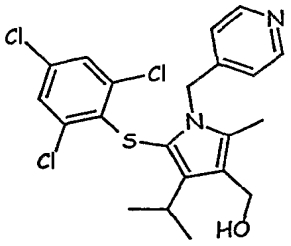
43		5-[4-(Trifluoromethoxy)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	436	1 different disulfide
44		5-(2,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	421	1 different disulfide
45		5-(3,5-Dichlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	449	1 using iPrCOCH2CO2Et
46		4-Isopropyl-2-methyl-5-(2-naphthylthio)-1[(4-pyridinyl)methyl]-1H-pyrrole-3-methanol	402	1 different disulfide
47		5-(2,4-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	421	1 different disulfide

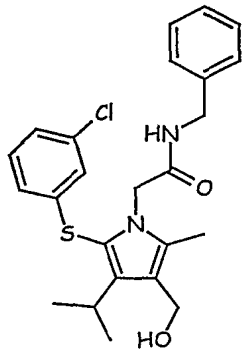
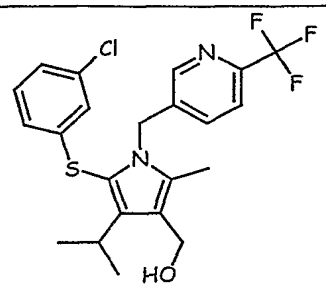
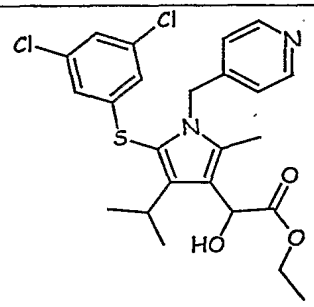
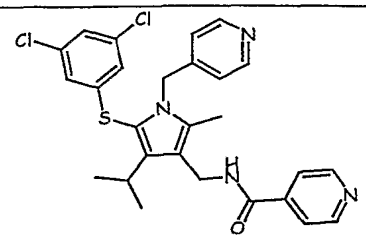
48		5-(3-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	370	1 different disulfide
49		5-(3-Chlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	415	1 using iPr2COCH2CO2Et
50		4-Isopropyl-5-(3,4-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	412	1 different disulfide
51		4-Isopropyl-2-methyl-5-(2,4,6-trimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	394	1 different disulfide
52		4-Isopropyl-2-methyl-5-(3,4-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	380	1 different disulfide

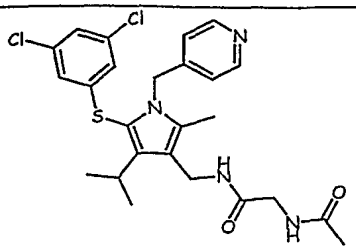
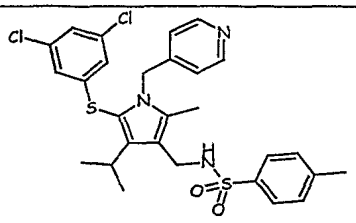
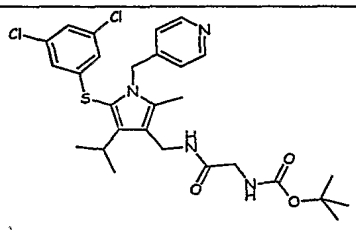
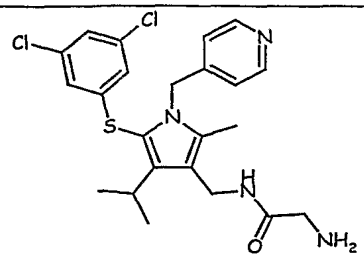
53		4-Isopropyl-5-(2,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	412	1 different disulfide
54		4-Isopropyl-2-methyl-5-(2,5-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	380	1 different disulfide
55		4-Isopropyl-5-(2-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	382	1 different disulfide
56		5-(2-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	370	1 different disulfide
57		4-Isopropyl-2-methyl-5-(4-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	366	1 different disulfide

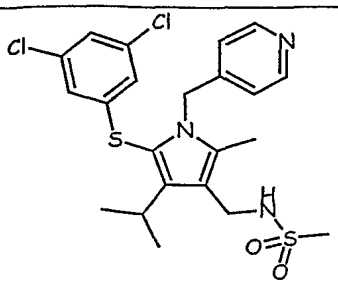
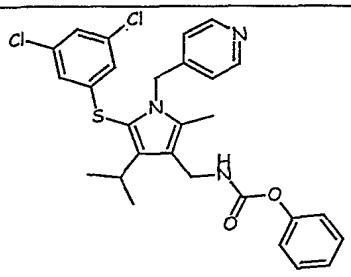
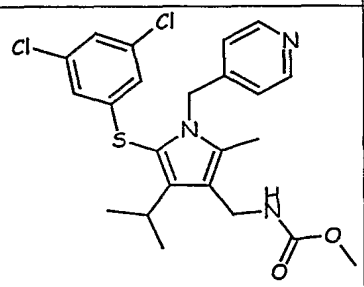
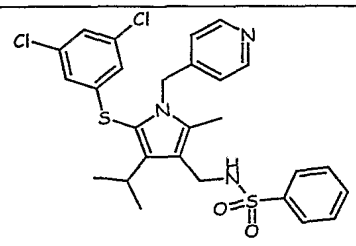
58		1-Benzyl-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	386	1 different disulfide
59		5-(3-Chlorophenylthio)-4-isopropyl-1-(4-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol	416	1 different disulfide and R1
60		5-(3-Chlorophenylthio)-4-isopropyl-1-(3-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol	416	1 different disulfide and R1
61		1-[(5-Chloro-1-benzothiophen-3-yl)methyl]-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	476	1 different disulfide
62		alpha(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]benzyl alcohol	497	1 using PhMgBr

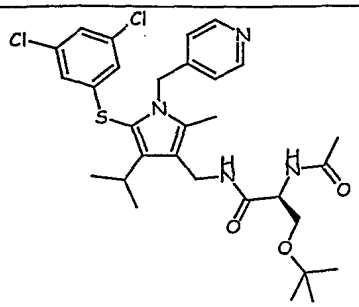
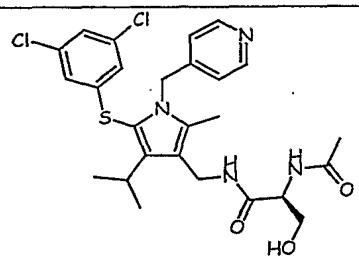
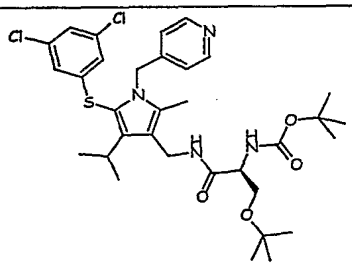
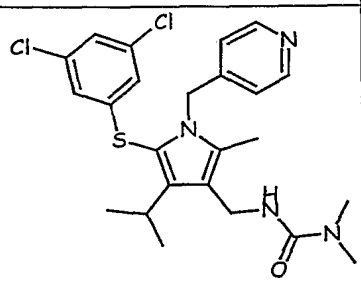
63		5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-thiazolyl)methyl]-1H-pyrrole-3-methanol	393	1 different disulfide and R1
64		5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(3-(4-pyridyl)propyl]-1H-pyrrole-3-methanol	415	1 different disulfide and R1
65		5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(2-quinolyl)methyl]-1H-pyrrole-3-methanol	437	1 different disulfide and R1
66		4-Isopropyl-2-methyl-5-(2,4-dimethylphenylthio) -1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	380	1 different disulfide
67		4-Isopropyl-2-methyl-5-(3-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	366	1 different disulfide

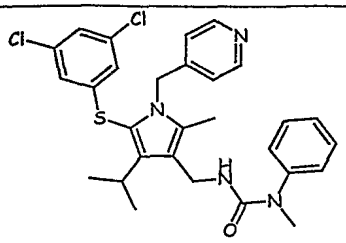
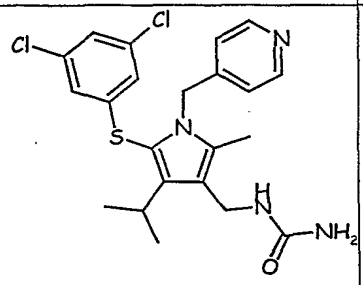
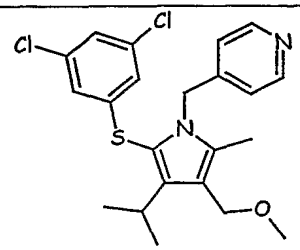
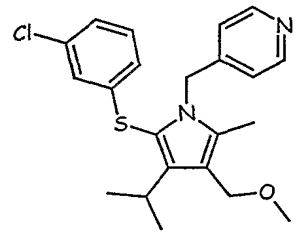
68		5-(2-Chloro-6-methylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	401	1 different disulfide
69		5-(3-Chlorophenylthio)-1-[[4-chloro-2-(trifluoromethyl)-6-quinolyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	539	1 different disulfide and R1
70		5-(4-Ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	380	1 different disulfide
71		4-Isopropyl-5-(3-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	382	1 different disulfide
72		5-(2,4,6-Trichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	496 [M+MeCN+H]+	1 different disulfide

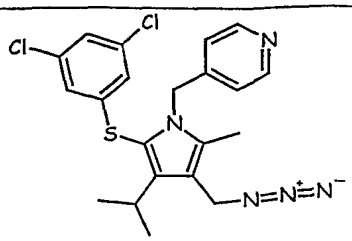
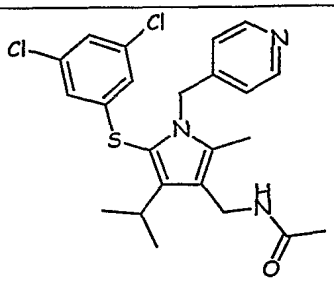
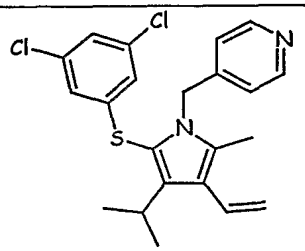
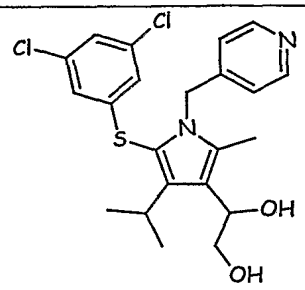
73		N-Benzyl-2-(3-chlorophenylthio)-4-(hydroxymethyl)-3-isopropyl-5-methyl-1-pyrroleacetamide	443	1 different disulfide and R1
74		5-(3-Chlorophenylthio)-1-[[6-(trifluoromethyl)-3-pyridyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol	455	1 different disulfide and R1
Compounds were prepared analogous to reaction scheme 2:				
75		[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-2-methyl-1-pyridin-4-ylmethyl-1H-pyrrol-3-yl]-hydroxy-acetic acid ethyl ester	493	2 (reduction of ketone)
76		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-4-pyridineacetamide	525	2

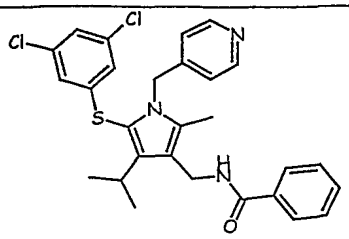
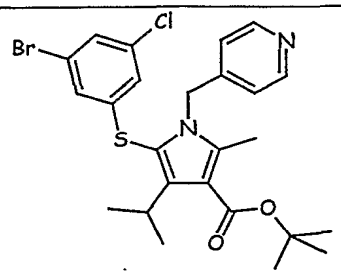
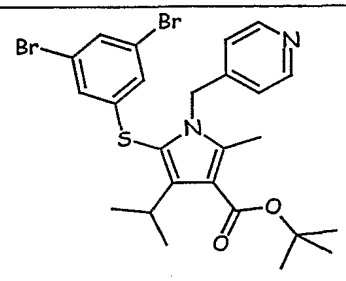
77		2-Acetamido-N-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide	519	2
78		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-p-toluenesulfonamide	574	2
79		tert.-butyl [[[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamoyl]methyl]carbamate	577	2
80		N2-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]glycinamide	477	2

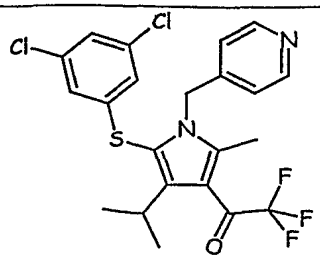
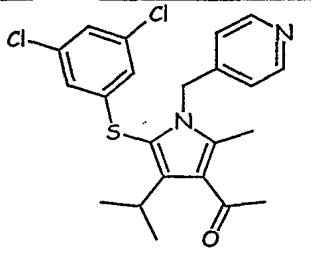
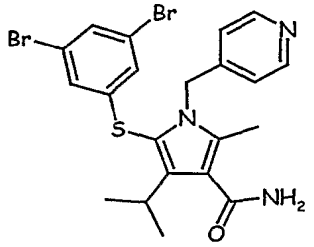
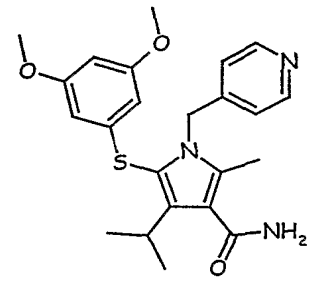
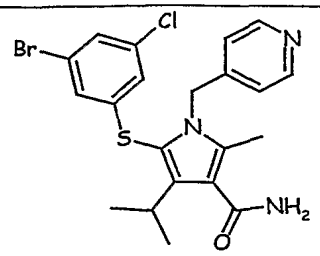
81		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl-1H-pyrrol-3-yl]methyl]methanesulfonamide	498	2
82		Phenyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate	540	2
83		Methyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate	478	2
84		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzenesulfonamide	560	2

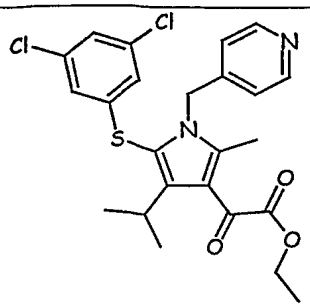
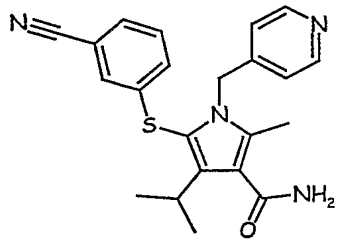
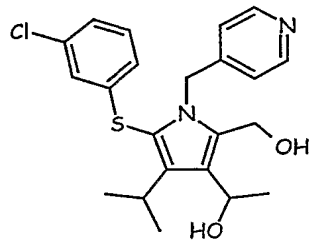
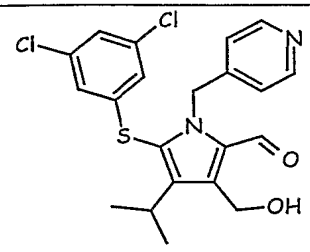
85		N1-Acetyl-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-ylmethyl]-L-serinamide	605	2
86		N1-Acetyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide	549	2
87		N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide	663	2
88		1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-3,3-dimethylurea	491	2

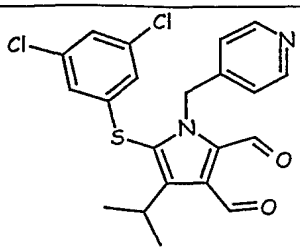
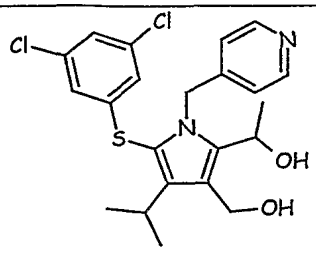
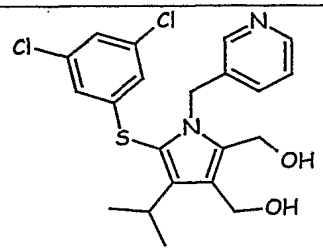
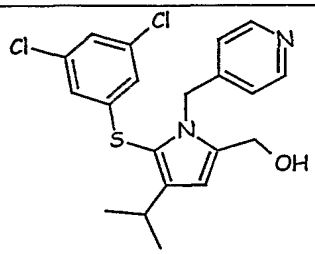
89		1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyriyl)methyl]-1H-pyrrol-3-yl]methyl]-3-methyl-3-phenylurea	553	2
90		1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]urea	463	2
91		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine	435	2
92		4-[[2-(3-Chlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine	401	2

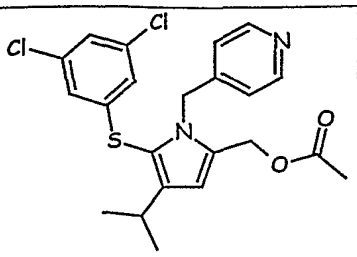
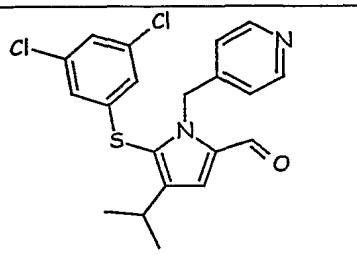
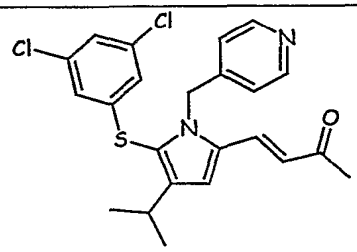
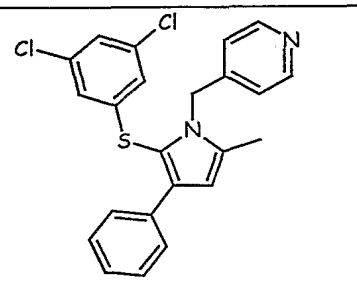
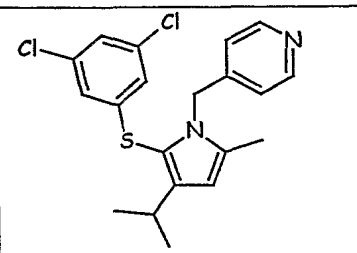
93		4-[[3-(Azidomethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridine	446	2
94		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide	462	2
95		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-4-vinyl-1-pyrrolyl]methyl]pyridine	417	2
96		1(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-1,2-ethanediol	451	2 from vinyl

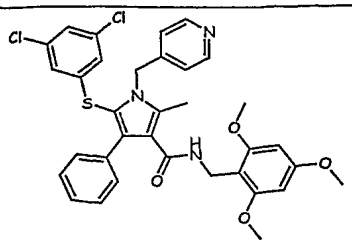
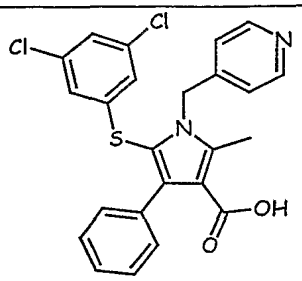
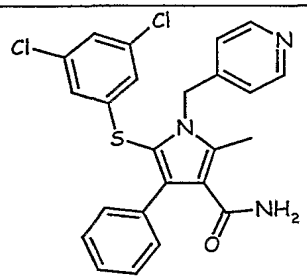
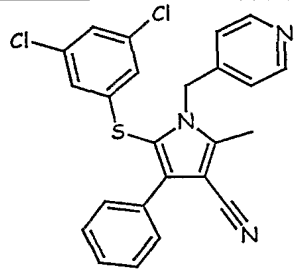
97		N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzamide	524	2
98		tert.-butyl 5-(3-bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate	536	2 tBu only difference
99		tert.-butyl 5-(3,5-dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate	580	2 tBu only difference
Compounds were prepared analogous to reaction scheme 3:				

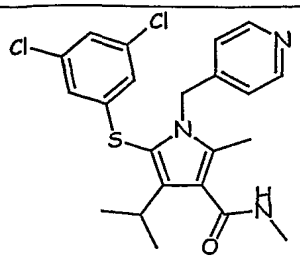
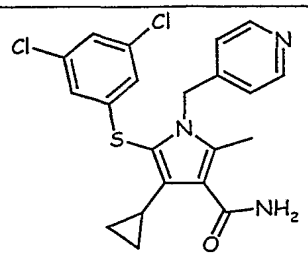
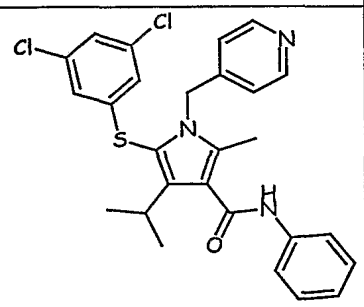
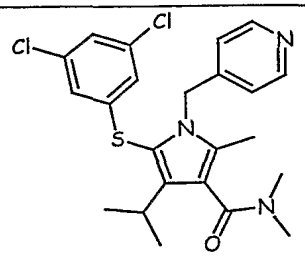
100		1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-2,2,2-trifluoroethanone	487	3 using CF3COCH2CO2Et
101		1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]ethanone	433	3 using CH2COCH2COCH3
102		5-(3,5-Dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	523	3 using different disulfide and NH2COCH2CO2Et
103		4-Isopropyl-5-(3,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	425	3 using different disulfide and NH2COCH2CO2Et
104		5-(3-Bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	480	3 using different disulfide and NH2COCH2CO2Et

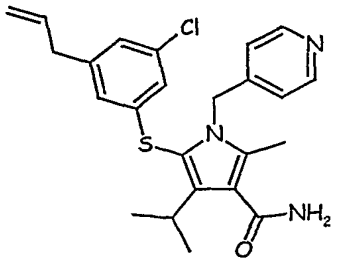
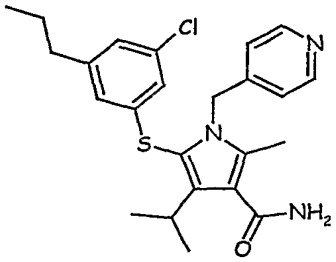
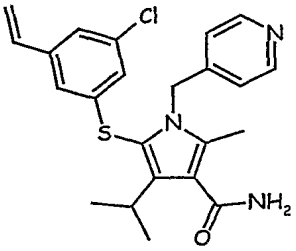
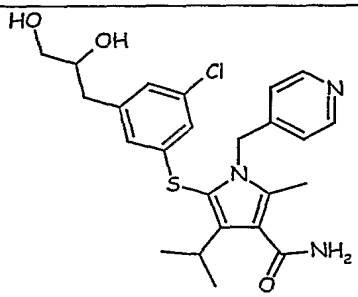
105		Ethyl 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-glyoxalate	491	3 using EtO2CCOCH2CO2Et
106		5-(3-Cyanophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	390	3 using different disulfide and NH2COCH2CO2Et
Compounds were prepared analogous to reaction scheme 6 or 7:				
107		5-(3-Chlorophenylthio)-2-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol	417	6
108		5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehyde	438	6

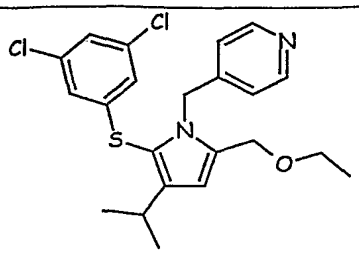
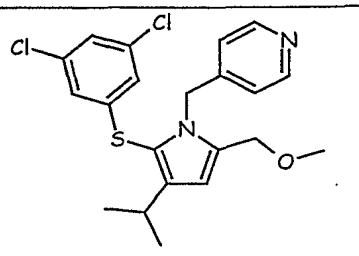
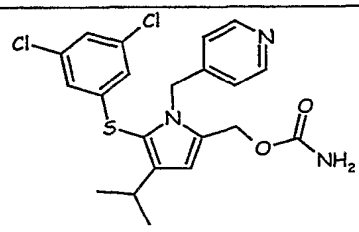
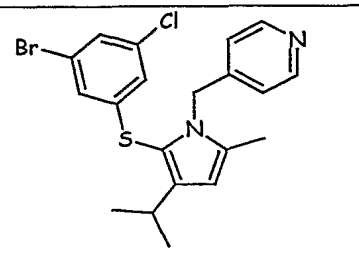
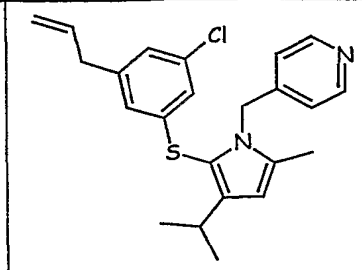
109		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-dicarboxaldehyde	433	6
110		5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-ethanol	451	6
111		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(3-pyridyl]methyl]-1H-pyrrole-2,3-dimethanol	437	6
Compounds were prepared analogous to reaction scheme 8 or 9:				
112		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol	407	8

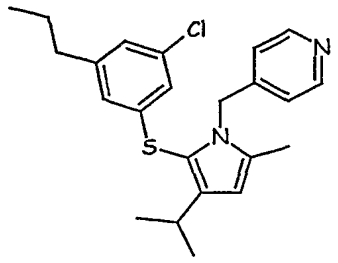
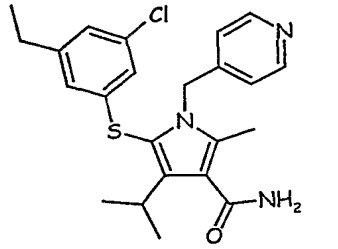
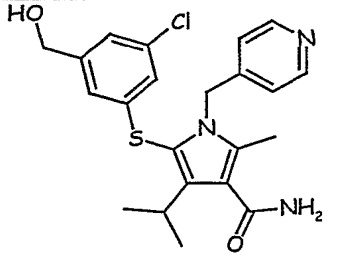
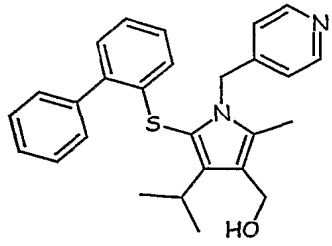
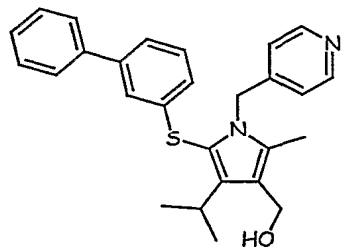
113		[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl acetate	447	8
113a		5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carbaldehyde	405	8
114		4-[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-pyrrol-2-yl]-but-3-en-2-one	445	8
115		4-[[2-(3,5-Dichlorophenylthio)-5-methyl-3-phenyl-1-pyrrolyl]methyl]pyridine	425	8
115a		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine	391	8

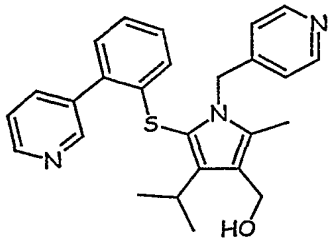
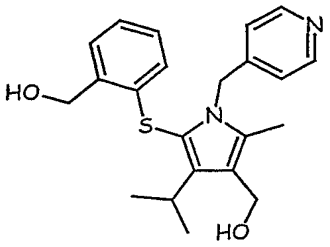
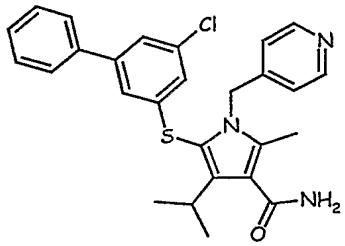
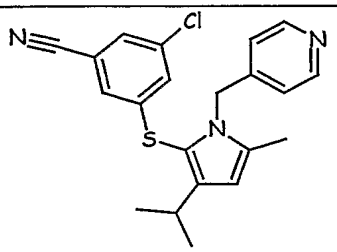
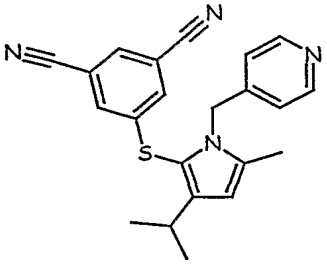
116		5-(3,5-Dichlorophenylthio)-N-(2,4,6-trimethoxybenzyl)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	648	8
117		5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid trifluoroacetate (1:1)	469	8
118		5-(3,5-Dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	468	8
119		5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carbonitrile	450	8

120		5-(3,5-Dichlorophenylthio)-4-isopropyl-N,2-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	448	8
121		5-(3,5-Dichlorophenylthio)-4-cyclopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	432	8
122		5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxanilide	510	8
123		5-(3,5-Dichlorophenylthio)-4-isopropyl-N,N,2-trimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	462	8

124		5-(3-Allyl-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	440	8
125		5-(3-Chloro-5-propylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	442	8
126		5-(3-Chloro-5-vinylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	426	8
127		5-[3-Chloro-5-(2(RS),3-dihydroxypropyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	474	8

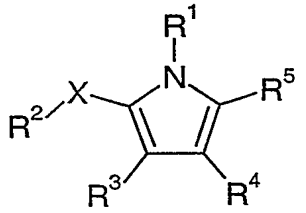
128		4-[[2-(3,5-Dichlorophenylthio)-5-(ethoxymethyl)-3-isopropyl-1-pyrrolyl]methyl]pyridine	435	8
129		4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-(methoxymethyl)-1-pyrrolyl]methyl]pyridine	421	8
130		[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl carbamate	450	8
131		4-[[2-(3-Bromo-5-chlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine	435	8
Compounds were prepared analogous to reaction scheme 10				
132		4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridine	397	10

133		4-[[2-(3-Chloro-5-propylphenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine	399	10
134		5-(3-Chloro-5-ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	428	10
135		5-[3-Chloro-5-(hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	430	10
136		5-(2-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-methanol	428	10
137		5-(3-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	428	10

138		4-Isopropyl-2-methyl-1-[(4-pyridyl)methyl]-5-[2-(3-pyridyl)phenylthio]-1H-pyrrole-3-methanol	429	10
139		5-[2-(Hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol	382	10
140		5-(5-Chloro-3-biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide	476	10
141		3-Chloro-5-[3-isopropyl-5-methyl-1-[(4-pyridinyl)methyl]-1H-pyrrol-2-ylthio]benzonitrile	382	10
142		5-[3-Isopropyl-5-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-ylthio]-1,3-dibenzonitrile	372	10

Claims

1. Compounds of formula I



I

wherein

R^1 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^2 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^3 is hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R, CONR'R", cyano or alkenyl, wherein

R is hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl, and wherein

R' and R", are independently of each other, hydrogen, alkyl or aryl;

R^5 is alkyl, aryl or a group -Z-C(=O)R"', wherein

Z is a single bond or –CH=CH-, and wherein

R"' is hydrogen or alkyl;

X represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that

only one of R^3 and R^4 is hydrogen and alkyl in R^3 is not CF_3; and

hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof.

2. Compound as claimed in claim 1 wherein

R^1 is alkyl;

R^2 is alkyl or aryl;

R^3 is alkyl, cycloalkyl or aryl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R, CONR'R", cyano or alkenyl, wherein

R is hydrogen, alkyl, alkoxy, trifluoromethyl, methyl-oxy-carbonyl or ethyl-oxy-carbonyl, and wherein

R' and R", are independently of each other, hydrogen, alkyl or aryl;

R^5 is alkyl, aryl or a group -Z-C(=O)R"', wherein

Z is a single bond or –CH=CH-, and wherein

R"' is hydrogen or alkyl;

X represents S, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that

alkyl in R^3 is not CF_3.

3. Compounds as claimed in any one of claims 1 to 2 wherein

R^1 is C_{1-7} alkyl or C_{1-7} alkyl substituted with 1-3 substituents selected from cycloalkyl, aryl and heterocyclyl;

R^2 is C_{1-7} alkyl, phenyl or phenyl substituted with 1-5 substituents selected from C_{1-7} alkyl, halogen and nitro;

R^3 is C_{1-7} alkyl, phenyl, C_{1-7} alkyl substituted with 1-3 heterocyclyl or phenyl substituted with 1-5 substituents selected from C_{1-4}-alkyl, C_{1-4}-alkoxy and halogen;

R^4 is hydrogen, C_{1-7} alkyl or C_{1-7} alkyl substituted with 1-3 substituents selected from hydroxy, amino, C_{1-4}-alkoxy, phenyl, methyl-oxy-carbonyl, ethyl-oxy-carbonyl, azido, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-

amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, methyl-sulfonyl-amino, phenyl-sulfonyl-amino, p-toluyl-sulfonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide;

R^5 is C_{1-7} alkyl, phenyl or C_{1-7} alkyl substituted with 1-3 substituents selected from hydroxy, C_{1-4}-alkoxy, methyl-carbonyl-oxy and amino-carbonyl-oxy;

X represents S, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl.

4. Compounds as claimed in any one of claims 1 to 3 wherein

R^1 is methyl, ethyl, isopropyl, cyclohexylmethyl, phenylmethyl, pyridylmethyl;

R^2 is methyl, n-propyl or phenyl substituted with 1-5 chlorine atoms;

R^3 is isopropyl, n-propyl or pyridylmethyl;

R^4 is hydrogen or C_{1-2} alkyl substituted with 1-3 substituents selected from hydroxy, amino, C_{1-2}-alkoxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide;

R^5 is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert.-butyl or C_{1-2}-alkyl substituted with 1-3 substituents selected from hydroxy, C_{1-2}-alkoxy, methyl-carbonyl-oxy and amino-carbonyl-oxy;

X represents S, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl.

5. Compounds as claimed in any one of claims 1 to 4 wherein

R^1 is 4-pyridylmethyl;

R^2 is methyl or 3,5-dichlorophenyl;

R^3 is isopropyl;

R^4 is C_{1-2} alkyl substituted with 1-2 substituents selected from hydoxy, 2-pyridyl-carbonyl-amino, 3-pyridyl-carbonyl-amino, 4-pyridyl-carbonyl-amino, (phenoxy)-carbonyl-amino, (methoxy)-carbonyl-amino, (di-methyl-amino)-carbonyl-amino, (phenyl-amino)-carbonyl-amino, (amino)-carbonyl-amino, (phenyl)-carbonyl-amino, (methyl)-carbonyl-amino, methyl-carbonyl-amino-methyl-carbonyl-amino, (tert.-butyl)-carbonyl-amino-methyl-carbonyl-amino, (N1-acetyl-O-tert.-butyl-N2-yl)-L-serinamide, (N1-acetyl-N2-yl)-L-serinamide and [N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-yl]-L-serinamide;

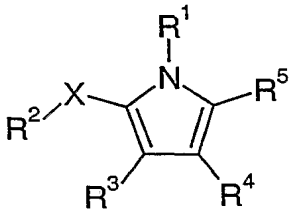
R^5 is methyl, ethyl, n-propyl, isopropyl or C_{1-2}-alkyl substituted with 1-3 substituents selected from hydroxy, methyl-carbonyl-oxy and amino-carbonyl-oxy;

X represents S, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl.

6. Compounds as claimed in any one of claims 1 to 5 wherein

X represents S.

7. Compounds of formula I



I

wherein

R^1 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^2 is alkyl, cycloalkyl, aryl or heterocyclyl;

R^3 is hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl;

R^4 is hydrogen, alkyl, carboxyl, C(=O)R or $CONR_2$ wherein

R is hydrogen or alkyl;

R^5 is hydrogen or alkyl;

X represents S, S(O), $S(O)_2$, O, N(alkyl) or X-R^2 together represent CH_2-aryl or CH_2-heterocyclyl; and with the proviso that

only one of R^3, R^4 and R^5 is hydrogen and alkyl in R^3 is not CF_3;

hydrolyzable esters or ethers thereof or a pharmaceutically acceptable salt thereof.

8. Compound as claimed in claim 7 wherein

X represents S, S(O), $S(O)_2$, O, N(alkyl).

9. Compound as claimed in any one of claims 7 to 8 wherein

X represents S.

10. Compounds as claimed in any one of claims 7 to 9 wherein

R^1 is alkyl, R^2 is alkyl or aryl, R^3 is alkyl or aryl, R^4 is hydrogen, alkyl, carboxyl, C(=O)R or $CONR_2$.

11. Compounds as claimed in any one of claims 7 to 10 wherein

R^1 is alkyl substituted with heterocyclyl or aryl, unsubstituted C_{1-7} alkyl or alkyl substituted with cycloalkyl;

R^2 is unsubstituted alkyl, unsubstituted phenyl or substituted phenyl with 1 to 5 halogen or nitro or unsubstituted C_{1-7} alkyl as substituents;

R^3 is unsubstituted alkyl or substituted alkyl with heterocyclyl as substituent, unsubstituted phenyl or substituted phenyl with 1 to 5 halogen or methoxy or unsubstituted alkyl as substituents;

R^4 is hydrogen, unsubstituted alkyl or substituted alkyl with hydroxy or amino or methoxy as substituents, carboxyl, C(=O)R, $CONR_2$;

R^5 is hydrogen, unsubstituted alkyl or substituted alkyl with hydroxy as substituent;

X represents S.

12. Compounds as claimed in any one of claims 7 to 11 wherein

R^1 is pyridylmethyl, phenylmethyl, methyl, ethyl, isopropyl, cyclohexylmethyl;

R^2 is methyl, n-propyl or chlorinated phenyl;

R^3 is isopropyl, n-propyl or pyridylmethyl;

R^4 is methyl or ethyl with hydroxy or methoxy as substituents, carboxyl, C(=O)R, $CONR_2$;

R^5 is methyl or ethyl optionally substituted with a hydroxy group,

X represents S.

13. Compounds as claimed in any one of claims 7 to 12 wherein

R^1 is 4-pyridyl methyl;

R^2 is methyl or 3,5-dichlorophenyl;

R^3 is isopropyl;

R^4 is methyl substituted with a hydroxy group or C(=O)R;

R^5 is methyl;

X represents S.

14. Compounds as claimed in claim 7 selected from:

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxaldehyde,

5-(3,5-Dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1,2-dimethyl-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-1-ethyl-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

1-Benzyl-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

1-(Cyclohexylmethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(2-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-phenylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(3-nitrophenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dimethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-isopropylthio-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-methylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-(4-Chlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-methyl-4-(4-methylphenyl)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-(4-methoxyphenyl)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-(3,4-Dichlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4,5-dimethyl-1H-pyrrol-1-yl]methyl]pyridine,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylamine,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1H-pyrrol-1-yl]methyl]pyridine,

5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-ethyl-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenoxy)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-[(3,5-Dichlorophenyl)methylamino]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-Benzyl-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-1,5-bis[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-1-isopropyl-3-methyl-4-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-3-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol.

15. Compounds as claimed in claim 1 selected from:

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxaldehyde,

5-(3,5-Dichlorophenylthio)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1,2-dimethyl-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-1-ethyl-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

1-Benzyl-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

1-(Cyclohexylmethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(2-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-phenylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(3-nitrophenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dimethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-isopropylthio-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-methylthio-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-(4-Chlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-methyl-4-(4-methylphenyl)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-(4-methoxyphenyl)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-(3,4-Dichlorophenyl)-5-(3,5-dichlorophenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4,5-dimethyl-1H-pyrrol-1-yl]methyl]pyridine,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methylamine,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1H-pyrrol-1-yl]methyl]pyridine,

5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2-ethyl-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenoxy)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-[(3,5-Dichlorophenyl)methylamino]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-Benzyl-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-1,5-bis[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-1-isopropyl-3-methyl-4-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-3-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

5-(3,5-Dichlorophenylthio)-2,4-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(3-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2-chloro-4-fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-(4-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-[3-(Trifluoromethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-[4-(Trifluoromethoxy)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3,5-Dichlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(2-naphthylthio)-1[(4-pyridinyl)methyl]-1H-pyrrole-3-methanol,

5-(2,4-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-2,4-diisopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-(3,4-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(2,4,6-trimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(3,4-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-(2,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(2,5-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-(2-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2-Fluorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(4-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

1-Benzyl-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-1-(4-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-1-(3-methoxybenzyl)-2-methyl-1H-pyrrole-3-methanol,

1-[(5-Chloro-1-benzothiophen-3-yl)methyl]-5-(3-chlorophenylthio)-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

alpha(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]benzyl alcohol,

5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-thiazolyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(3-(4-pyridyl)propyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-4-isopropyl-2-methyl-1-[(2-quinolyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(2,4-dimethylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-5-(3-methylphenylthio)-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2-Chloro-6-methylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(3-Chlorophenylthio)-1-[[4-chloro-2-(trifluoromethyl)-6-quinolyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

5-(4-Ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-5-(3-methoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

5-(2,4,6-Trichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

N-Benzyl-2-(3-chlorophenylthio)-4-(hydroxymethyl)-3-isopropyl-5-methyl-1-pyrroleacetamide,

5-(3-Chlorophenylthio)-1-[[6-(trifluoromethyl)-3-pyridyl]methyl]-4-isopropyl-2-methyl-1H-pyrrole-3-methanol,

[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-2-methyl-1-pyridin-4-ylmethyl-1H-pyrrol-3-yl]-hydroxy-acetic acid ethyl ester,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-

3-yl]methyl]-4-pyridineacetamide,

2-Acetamido-N-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-p-toluenesulfonamide,

tert.-butyl [[[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamoyl]methyl]carbamate,

N2-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]glycinamide,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl-1H-pyrrol-3-yl]methyl]methanesulfonamide,

Phenyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate,

Methyl [[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]carbamate,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzenesulfonamide,

N1-acetyl-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-ylmethyl]-L-serinamide,

N1-acetyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide,

N1-(tert.-butoxycarbonyl)-O-tert.-butyl-N2-[[5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-L-serinamide,

1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]-3,3-dimethylurea,

1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyriyl)methyl]-1H-pyrrol-3-yl]methyl]-3-methyl-3-phenylurea,

1-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]urea,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine,

4-[[2-(3-Chlorophenylthio)-3-isopropyl-4-(methoxymethyl)-5-methyl-1-pyrrolyl]methyl]pyridine,

4-[[3-(Azidomethyl)-5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-pyrrolyl]methyl]pyridine,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]acetamide,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-4-vinyl-1-pyrrolyl]methyl]pyridine,

1(RS)-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-1,2-ethanediol,

N-[[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]methyl]benzamide,

tert.-butyl 5-(3-bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate,

tert.-butyl 5-(3,5-dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylate,

1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]-2,2,2-trifluoroethanone,

1-[5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-yl]ethanone,

5-(3,5-Dibromophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

4-Isopropyl-5-(3,5-dimethoxyphenylthio)-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3-Bromo-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

Ethyl 5-(3,5-dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-glyoxalate,

5-(3-Cyanophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3-Chlorophenylthio)-2-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-ethanol,

5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carboxaldehyde,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2,3-dicarboxaldehyde,

5-(3,5-Dichlorophenylthio)-3-(hydroxymethyl)-4-isopropyl-alpha(RS)-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-ethanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(3-pyridyl]methyl]-1H-pyrrole-2,3-dimethanol,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-methanol,

[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl acetate,

5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrole-2-carbaldehyde,

4-[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-pyrrol-2-yl]-but-3-en-2-one,

4-[[2-(3,5-Dichlorophenylthio)-5-methyl-3-phenyl-1-pyrrolyl]methyl]pyridine,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine,

5-(3,5-Dichlorophenylthio)-N-(2,4,6-trimethoxybenzyl)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxylic acid trifluoroacetate (1:1),

5-(3,5-Dichlorophenylthio)-4-phenyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3,5-Dichlorophenylthio)-2-methyl-4-phenyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carbonitrile,

5-(3,5-Dichlorophenylthio)-4-isopropyl-N,2-dimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3,5-Dichlorophenylthio)-4-cyclopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3,5-Dichlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxanilide,

5-(3,5-Dichlorophenylthio)-4-isopropyl-N,N,2-trimethyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3-Allyl-5-chlorophenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3-Chloro-5-propylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(3-Chloro-5-vinylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-[3-Chloro-5-(2(RS),3-dihydroxypropyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

4-[[2-(3,5-Dichlorophenylthio)-5-(ethoxymethyl)-3-isopropyl-1-pyrrolyl]methyl]pyridine,

4-[[2-(3,5-Dichlorophenylthio)-3-isopropyl-5-(methoxymethyl)-1-pyrrolyl]methyl]pyridine,

[5-(3,5-Dichlorophenylthio)-4-isopropyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-yl]methyl carbamate,

4-[[2-(3-Bromo-5-chlorophenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine,

4-[[2-(3-Allyl-5-chlorophenylthio)-3-isopropyl-5-methyl-[(4-pyrrolyl]methyl]pyridine,

4-[[2-(3-Chloro-5-propylphenylthio)-3-isopropyl-5-methyl-1-pyrrolyl]methyl]pyridine,

5-(3-Chloro-5-ethylphenylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-[3-Chloro-5-(hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

5-(2-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-3-methanol,

5-(3-Biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

4-Isopropyl-2-methyl-1-[(4-pyridyl)methyl]-5-[2-(3-pyridyl)phenylthio]-1H-pyrrole-3-methanol,

5-[2-(Hydroxymethyl)phenylthio]-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-methanol,

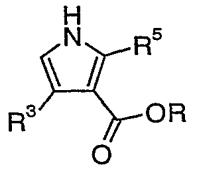
5-(5-Chloro-3-biphenylylthio)-4-isopropyl-2-methyl-1-[(4-pyridyl)methyl]-1H-pyrrole-3-carboxamide,

3-Chloro-5-[3-isopropyl-5-methyl-1-[(4-pyridinyl)methyl]-1H-pyrrol-2-ylthio]benzonitrile,

5-[3-Isopropyl-5-methyl-1-[(4-pyridyl)methyl]-1H-pyrrol-2-ylthio]-1,3-dibenzonitrile.

16. Process for the preparation of compounds of formula VIII

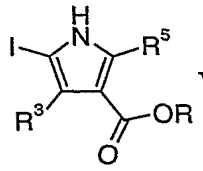
which process comprises reacting the compound of formula VII



VII

wherein R, R^3 and R^5 are as described in formula I

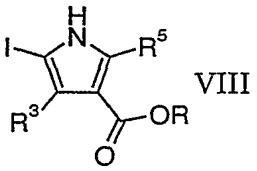
with a iodination agent to obtain the iodo pyrrole derivative of formula VIII



VIII

wherein R, R^3 and R^5 are as described in formula I

17. Compounds of formula VIII



VIII

wherein R, R^3 and R^5 are as described in formula I

18. A compound of formula I, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, or composition containing a compound of formula I, as claimed in any one of claims 1 to 15 for use as medicament.

19. Use of a compound of formula I, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, or composition containing a compound of formula I, as claimed in any one of claims 1 to 15 for the preparation of a medicament for the treatment of a disease mediated by the human immunodeficiency virus (HIV).

20. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15 and, if desired, a pharmaceutical inert carrier.

21. A process for preparing a medicament, which process comprises bringing a compound, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15 into a galenical administration form together with a pharmaceutical inert carrier.

22. Use of a compound, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, in the treatment of a disease mediated by the human immunodeficiency virus (HIV).

23. A method of treating a disease mediated by the human immunodeficiency virus (HIV) in a subject, which method comprises administering to said subject a pharmaceutically effective amount of a compound, or hydrolyzable ester, ether or pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15.

5

24. The invention as herein before described.

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INTERNATIONAL SEARCH REPORT

	cation No
	PCT/EP 01/04832

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/36 C07D401/06 A61K31/44 A61K31/40 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 644 631 A (PACHTER IRWIN J ET AL) 22 February 1972 (1972-02-22) cited in the application Starting materials i.e. H instead of C(O)aryl column 3, line 65 - line 70	1-18
E	DE 199 63 174 A (GRUENENTHAL GMBH) 12 July 2001 (2001-07-12) page 1, line 19 - line 26; claim 1	1-18
A	WO 98 02430 A (SAKAKIBARA MINORU ;PFIZER PHARMA (JP); KAWAI AKIYOSHI (JP); KAWAI) 22 January 1998 (1998-01-22) claim 1	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2001	20/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

INTERNATIONAL SEARCH REPORT

I Application No
PCT/EP 01/04832

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 959 074 A (PFIZER) 24 November 1999 (1999-11-24) claim 1	1-18
A	WO 95 33727 A (PFIZER ;BRIGHT GENE M (US); WELCH WILLARD M JR (US)) 14 December 1995 (1995-12-14) claim 1	1-18
A	US 4 282 242 A (HOLLAND GERALD F) 4 August 1981 (1981-08-04) cited in the application Compounds (II) claim 1	1-18
A	WO 96 18628 A (UPJOHN CO ;ROMERO DONNA L (US); THOMAS RICHARD C (US); MAY PAUL D) 20 June 1996 (1996-06-20) claim 1	1-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 24

Claim 24 is completely superfluous in so far as it refers to previous claims. In so far as it refers to the description this is not allowable under Rule 6.

Present claims 1-23 relate to a products defined by reference to a desirable characteristic or property, namely that they are"hydrolysable esters or ethers". The said claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

These are functional definitions which attempts to define a chemical compound in terms of a result to be achieved. This is not allowable. The said terms have not been searched and should be deleted. They are functional definitions without a specific technical guidance for the selection of the suitable derivatives in the description and without proven general knowledge to show which derivatives are suitable esters or ethers. The terms could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants. In such a situation, when the invention cannot be carried out over the whole claimed area without imposing an undue burden, the disclosure may be considered insufficient in the sense of Art 5, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds (I), but not the "hydrolysable esters or ethers" thereof.

There is an unacceptable discrepancy between the claims and the description since the description (see pages 3-13) makes it clear that various hydrocarbon substituents can be substituted. The skilled person would not have been aware of this from a reading of the claims since the skilled person would assume that standard IUPAC nomenclature was being used. In the current case, however, the Applicant has obviously seen fit to use non-standard nomenclature. The intended scope of the claims cannot be understood without referring to the description which contravenes (Rule 6 PCT). The scope of the invention as defined by the description can be described as being such that essentially any substituent in (I) in claim 1 is to be considered as optionally substituted.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This means that the claims, in the light of the description, should presumably be understood to cover an infinitely large number of possible compounds. In fact, the claims contain so many possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search as regrds the optional substitution of R1-R4 has been limited to sustitution as defined in claim 3. Additionally the vast scope of the claims cannot be considered to represent matter for which there is full support and disclosure since the claims represent an overgeneralisation of the claims. The search has been limited to the clearly preferred compounds i.e. those where X is S (as in claims 6 or 9) and R2is 4-pyridyl methyl as in claims 4 and 13. Only such compounds have been searched. This covers the vast majority of the examples and in particular of those examples for which physical data has been provided.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

..nformation on patent family members

Application No
PCT/EP 01/04832

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3644631 A	22-02-1972	NONE	
DE 19963174 A	12-07-2001	WO 0147878 A	05-07-2001
WO 9802430 A	22-01-1998	AU 3044197 A	09-02-1998
		BR 9710352 A	17-08-1999
		CA 2260213 A	22-01-1998
		EP 0912548 A	06-05-1999
		HR 970378 A	31-08-1998
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